1958

Eugenics Quarterly

Vol. 5 March, 1958 No. 1

SPECIAL ISSUE

HEREDITY COUNSELING SYMPOSIUM

Sponsored by the American Eugenics Society

Morning Session: GENETICS IN MEDICAL PRACTICE
Chairman: JOHN C. BUGHER, M.D.
Director, Medical Education and Public Health
The Rockefeller Foundation

Afternoon Session: HEREDITY COUNSELING PANEL
Chairman: BENTLEY GLASS
Department of Biology
Johns Hopkins University

American Eugenics Society, Inc.

AMERICAN EUGENICS SOCIETY

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Eugenics Quarterly

Published by the AMERICAN EUGENICS SOCIETY, Inc.
230 Park Avenue, New York 17, N. Y.

Vol. 5, No. 1 March, 1958

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HELD AT THE NEW YORK ACADEMY OF MEDICINE BUILDING

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EUGENICS QUARTERLY is published March, June, September, and December at 3110 Elm Ave., Baltimore 11, Md., for the American Eugenics Society, Inc., Room 1523, 230 Park Avenue, New York 17, N. Y. EUGENICS QUARTERLY is mailed to all members of the Society and to non-member subscribers. Subscription price $3.00 per year. Inquiries about membership in the American Eugenics Society should be addressed to the Secretary of the Society, 230 Park Avenue, New York 17, N. Y. Single current copies, 75 cents; single back issue copies, $1.50.

THE X INTERNATIONAL CONGRESS OF GENETICS

The X International Congress of Genetics will be held at McGill University, Montreal, Canada, from August 20-27, inclusive, 1958. Congress Committees are now actively preparing for your arrival and raising funds for travel grants, particularly for overseas geneticists.

The program will include symposia, invited papers, short contributed papers, demonstrations, other meetings and exhibits. There will be a special exhibit on "The Role of Genetics in the Service of Man." Also, we are preparing an interesting program for the ladies and children and the latter will be cared for in a "Progeny Park."

Pre- and post-Congress tours both local and extending through eastern parts of Canada and the United States are being arranged. University residences, hotels, tourist homes or camping facilities can be arranged for members and their families.

Overseas transportation should be arranged very soon as travel accommodation is already being heavily booked for 1958. Family travel plans should be investigated.

If there is any possibility that you will be able to attend, we ask you to fill in the information requested below and send it to us *immediately*.

THE SECRETARY GENERAL

Professor J. W. Boyes,
Department of Genetics,
McGill University,
Montreal 2, P.Q., Canada.

Please send me further information regarding the X International Congress of Genetics.

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Vol. 5, No. 1, March, 1958 *Eugenics Quarterly*

HEREDITY COUNSELING SYMPOSIUM

Sponsored by

The American Eugenics Society

at

THE NEW YORK ACADEMY OF MEDICINE BUILDING

GENETICS IN MEDICAL PRACTICE

Morning Session

Chairman: *John C. Bugher, M.D.*
Director, Medical Education and Public Health
The Rockefeller Foundation

CHAIRMAN BUGHER: Will the meeting come to order, please.

I would like to call your attention to some aspects of the subject material of today's Symposium on Heredity Counseling and to something of the importance and significance of its function.

I suppose there is no region of human experience which has quite the same content of emotional overtone as the relation of parent to child. Most people are far more concerned about the welfare of their children than they are about their own health and happiness. Consequently, the functions which we are discussing in these symposia of the morning and the afternoon fall among those that come closest to the lives of people and their sense of values in the life of the individual as well as in the life of the family.

In genetic counseling one finds there are serious problems involved. I think we can say that the responsibility of the counselor falls into two distinctly different areas. One is the scientific content of his special field, the knowledge of genetics, and particularly the knowledge of human genetics. Despite the contrary opinions which are frequently expressed, I think that most of us feel that the objective of genetics research is to understand more completely—I don't say the only objective, but the chief objective—the manner of inheritance of human characteristics and factors that enter into the manifestation of those characteristics as the human individual develops. All of our genetics research, whether it is in agriculture, general biology, or whatever field, comes to bear on the problem of human inheritance.

Speaking of human genetics, here is a field of extreme difficulty. Those of you who have worked in the field are quite aware, and need no reminding, of the fact that the life span of the human being is of such length that it is difficult to get adequate data in terms of generations. This science rests very definitely upon a statistical basis, and we are confronted with various definitions of likelihood of events and

levels of probability beset with uncertainties. It is this whole background of scientific knowledge and lack of knowledge, of qualitative information, and uncertainty as to the trend of conclusions which may be applicable to man, that the counselor must keep in mind. For he has essentially a second relationship — that of the physician to his patient — a responsibility for the accuracy of his advice and a responsibility for the results of his advice, in a matter which falls so intimately into the reasons why people make certain choices. The responsibility of the adviser here, I think, comes very squarely within the general responsibility of a physician to his patient.

I don't know whether the question of malpractice will ever come up in regard to genetics counseling, but it's not to be put aside lightly as a reminder—not of a legal responsibility but of a moral responsibility which the counselor has in this very intimate and privileged relationship.

I think that as the morning progresses and as the discussion extends from purely morphologic aspects of human genetics through more functional aspects to the purely functional problems as we find them in psychiatry, we will probably become more appreciative of the importance of more adequate knowledge; and the significance of the use of this knowledge in human relationships will tend to emerge.

I will ask each speaker to be prepared for questions and discussion of his paper at the end of the presentation, and we will have to be a little hard, perhaps, in regard to time, because of the number of papers to be presented.

The first presentation, on "The Need for Parental Counseling in Pediatrics," is by Dr. Warkany, who is Professor of Research Pediatrics at the University of Cincinnati, and, I believe, known to very many in this room for his long and distinguished career in this general field of pediatrics, and especially with relation to some of these very difficult problems.

THE NEED FOR PARENTAL COUNSELING IN PEDIATRICS

Josef Warkany, M.D.
Children's Hospital Research Foundation
Cincinnati, Ohio

To discuss the pediatrician's point of view on Genetic Counseling represents a great challenge and responsibility, especially if this is to be done before expert geneticists by one who cannot claim to be a geneticist himself. A pediatrician interested in prenatal factors responsible for diseases and disorders of childhood has a great deal in common with those interested in human genetics. He believes, of course, in hereditary factors which cause or predispose to human illness and he knows that such factors must always be kept in mind when disorders of prenatal origin are under consideration. He, like the geneticist, is interested in prenatal preventive measures which could reduce the suffering of children and their parents. At the present time parental counseling is among the few preventive measures available for this purpose. However, it is to be expected that the pediatrician's point of view will differ in some respects from that of the geneticist. The two specialties encounter different samples of children, of diseases and of questions.

In discussing the need for parental counseling, I could choose the easy way out

by emphasizing the role of heredity in disorders of childhood. It would not be difficult to enumerate a long list of disorders which are dominated in their etiology by genetic factors and which lend themselves well to genetic counseling. Such a discussion would probably guarantee general approval, but it would also guarantee a boring talk. On the other hand, stressing points of possible disagreement between the pediatrician and the geneticist may provoke a lively controversy and bring about a better understanding of the differing points of view. I am sure this will be a friendly controversy since we all have the same aims though we may disagree on methods, terminology or explanation of the facts.

There can be no doubt about the great need for parental counseling in the fields of congenital malformations, mental retardation, convulsive disorders, blood dyscrasias, diabetes and many other diseases. In spite of this need it is not always easy to give satisfactory advice under the circumstances encountered in a pediatric hospital or office. Since I see chiefly children with congenital malformations or mental retardation I shall illustrate some of the difficulties with examples of these two groups.

Chondrodystrophy or achondroplasia is, according to the textbooks, a Mendelian dominant with high penetrance, and many pedigrees have been published which support this conception. One can see sometimes one or two children with this disorder in one family in which one parent has also chondrodystrophy. In such a situation a reasonably reliable prognosis can be made for future children in the family and for the future offspring of the affected children. However, the majority of children seen with chondrodystrophy by us do not conform to this simple scheme. First, one sees children with typical chondrodystrophy whose parents are normal and who appear in the pedigree as sporadic cases. Of course, such sporadic appearance does not rule out genetic determination. The sporadic case may be due to a new mutation and the affected child could transmit the disorder to his offspring, each child of the next generation having a 50:50 chance to be affected. It is very unlikely that the normal parents of the sporadic case will have another child with chondrodystrophy, since it is improbable that an identical mutation will occur in the same couple. Yet chondrodystrophy can occur twice in the offspring of parents who appear entirely normal. A child born at one of our hospitals showed short extremities and chondrodystrophy in roentgenograms. The parents and siblings were normal. If this case had been attributed to mutation, this would have largely precluded a repetition of the disorder in this family. However, one year later, a sibling of this child was born showing the same anomalies. Cases of recessive chondrodystrophy have been described, and we assume that our two cases in one family were also due to recessive inheritance. Some types of recessively inherited chondrodystrophy, such as the Ellis van Creveld syndrome or *chondrodystrophia calicificans,* are sufficiently distinctive to be separated from the dominant form, but others are not. These cannot always be recognized by clinical examination and may—in the case of the first affected child in the family—lead to erroneous interpretation and counseling. Morquio's disease, when fully developed, can be easily distinguished from classical chondrodystrophy. But even this well-established form may cause difficulties in parental counseling, since typical findings may be absent in early life. A baby born in one of our hospitals was suspected of chondrodystrophy because of disproportionate development of head, trunk and extremities. The arms and legs appeared short and fat, but X-rays revealed rather slender long bones. The parents were tall and well built and 4 older siblings were healthy and normal. When the roentgenograms were repeated 8 months later, changes in the spine and

the hip joints suggested Morquio's disease, which is attributed to a recessive gene. It seemed advisable then to warn the parents that the condition of the youngest child might be repeated in a subsequent child. The warning came late, since the mother was pregnant again. In this case, doubt about the diagnosis prevented a warning in time. Fortunately our omission was rectified by a favorable assortment of the parental germ cells at the right time and the sixth pregnancy ended happily with the birth of a normal child. I enumerated five systemic bone diseases which may have to be considered in the differential diagnosis of chondrodystrophy and know of others which have puzzled us at times. These forms represent entities of different etiologic origins. Yet chondrodystrophy is treated in some of the texts on genetics or genetic counseling as an etiologic entity permitting uniform genetic prognosis and eugenic advice.

It is almost certain that other congenital malformations which we consider as clinical entities are equally heterogeneous in origin. Hydrocephalus, microcephalus, oxycephalus, microphthalmus, cataract, cleft lip, cleft palate, dislocation of the hip, clubfoot, polydactylism and many others belong in this category. It seems that each of these malformations is merely a symptom which can be the result of different genetic mechanisms or the result of non-genetic prenatal disturbances.

Geneticists have recognized these difficulties of etiologic interpretation and have worked out empiric risk figures for various defects. Although the meaning of risk figures will be discussed by qualified members of the afternoon panel, I must mention here that they cannot be a substitute for specific etiologic diagnosis. The use of risk figures represents a definite step forward in genetic counseling, but it should not be considered a final method. If we admit that many of the malformations encountered are not etiologic entities but merely symptoms, then empiric risk figures derived from pools of heterogeneous cases may be far off when applied to a specific case. It is said, for instance, that cleft palate (without cleft lip) in a child of normal parents represents a 2 per cent risk for a sibling. Does this risk figure also apply to the sibling of a child with cleft palate and mandibulo-facial dysostosis? In the family of one of our cleft palate patients mandibulo-facial dysostosis was inherited like a dominant trait. The chance for a subsequent child to have mandibulo-facial dysostosis is 50:50. From the literature and our small experience with this syndrome it would appear that cleft palate is not rare in patients with mandibulo-facial dysostosis and that the risk for a subsequent child in this family having cleft palate is greater than 2 per cent. In another case of cleft palate the risk figure for a sibling is probably zero. In this case we can attribute the cleft palate to a chemical substance, aminopterin, which the mother took as an abortive in the second month of pregnancy. Since the mother is not likely to repeat this experiment, the eugenic prognosis for subsequent children should be good. These examples show that cleft palate is not an entity as regards etiology and eugenic prognosis; they indicate that we must try to ascertain the etiologic factors in individual cases and to replace general risk figures by risk figures specific for every single entity. It is obvious that we are not yet able to do this and that we have a great deal to learn about diagnosis, classification and etiology of congenital malformations before we can give reliable advice in individual cases.

In the field of mental retardation the situation is even more complicated. Gone are the days when feeble mindedness was attributed to one genetic unit character and when it was discussed as a dominant or a recessive "taint." Several years ago Gibson enumerated about 70 separable types of mental retardation. This must represent an underestimate, since new syndromes are described annually and added to this list.

We now think that each of these syndromes or each causative factor must be evaluated separately and that in some of the cases a sound eugenic prognosis is possible. Mental retardation caused by inborn errors of metabolism represents a facet particularly favored by investigators at the present time. The adverse effects of the metabolic error that causes phenylketonuria, a representative of this group, may be alleviated and even prevented by dietary means. Since this metabolic disorder can be attributed to a single recessive gene, it would lend itself to eugenic counseling if carriers could be discovered by chemical methods. The phenylalanine tolerance test used by Hsia and coworkers showed that, in general, the parents and some of the siblings of the affected children have reduced tolerance for phenylalanine. These findings have been confirmed in other laboratories, but it has been shown also that a few of the parents have normal or nearly normal tolerance curves. This indicates that we are not ready yet to counsel with certainty prospective parents who are possible carriers of this abnormal gene, with the help of this chemical test. Nonetheless, the work on phenylpyruvic oligophrenia has justly aroused great hopes in the field of mental retardation and points the way for future investigations along these lines. At the present time, however, we are not able yet to diagnose and classify the majority of cases of mental retardation, in spite of the many types that have been established as separate entities. If faced with a congenital sporadic case of undetermined origin, we must not consider him uncritically as a "mutation" or as the result of recessive inheritance. We must take into consideration that prenatal infections with viruses or protozoa, prenatal physical or chemical disturbances, interruption of the blood flow or anoxia, hemorrhages or birth traumas can also account for impairment of mental development. Sometimes the history obtained gives no clue, and at other times the history supplies three or four possible causes of the child's retardation. Needless to say that in either situation the etiology remains obscure and counseling difficult.

I have stressed so far what Fraser has called the "darker side" of heredity counseling, since it seems preferable to emphasize in a symposium like ours what has to be done rather than what has been done. Although the pediatrician interested in prenatal factors may be critical of some oversimplifications expressed by genetic counselors, his attitude should not be considered as negativistic. He recognizes the need for rational parental counseling, but he also recognizes the need for better knowledge in the diagnosis, classification and causation of disorders for which counsel is sought. He welcomes the existence of clinics where parents can obtain counsel for family planning, but he wonders why such clinics are called "heredity clinics" or why the counseling should be limited to "genetic counseling." It seems there is now general agreement that many of the disorders discussed can be brought on by genetic or non-genetic factors or by both. Why then prejudice the case by calling an advisory clinic a "heredity clinic" although it will deal in many instances with non-hereditary conditions? The pediatrician suggests, therefore, that a "clinic for parental counseling" would be more adequate for the purpose than a "heredity clinic." He suggests that parental counseling should be done by a team that includes geneticists but also pediatricians well-versed in the diagnosis, variability and nosology of the disorders to be evaluated. The team should also contain other specialists who can be consulted in appropriate cases. Hematologists, virologists and immunologists could make valuable contributions. I believe that such teams will be research teams for some time to come. For the time being it would seem preferable to have a limited number of clinics with highly qualified staffs drawn from many disciplines than to spread the avail-

able talent too thin. It should not be too difficult to find pediatricians to join such clinics, since there is more interest in genetic and other prenatal factors among pediatricians today than at any time before.

DISCUSSION

CHAIRMAN BUGHER: This very interesting paper is now open for discussion and questions.

DR. GORDON ALLEN: Dr. Warkany, you said that the phenylalanine tolerance test had not proven entirely reliable in the laboratories. I wonder if they have used simple levels of phenylalanine, or have they used the phenylalanine-tyrosine ratio?

DR. WARKANY: I don't know all the details. My knowledge comes from the Cincinnati experiments which will be published soon.

Most of the parents of the phenylpyruvic children that we could examine had higher curves in phenylalanine tolerance tests than the controls, but there was one father whose curve was within the normal range. And I heard that in another study both parents of a child with phenylketonuria had normal curves. I think the answer is that the phenylalanine tests do not yet go to the root of the abnormal metabolic error but is just one reaction we can measure.

DR. EDITH POTTER: I would like to comment on how well I think Dr. Warkany has set the stage for the meeting today. Certainly, the thing he has talked about this morning and so often in the past—the frequent inability to distinguish between genetic and environmental factors—is what we must all bear in mind.

Furthermore, the difficulty of diagnosis means that we should have more people who are really able to make a diagnosis attached to whatever counseling centers we have. I have been interested in the fact that many people feel able to make a statement in writing at a long distance on the chondrodystrophies that Dr. Warkany talked about, which seem to be currently of tremendous interest as far as genetic counseling is concerned. I have had a number of letters in the last few months saying, "What are the prospects for future pregnancies, with simply a statement that the chrondrodystrophy exists. Most people seem to think chrondrodystrophy is a single entity and that all cases could be expected to follow the same patterns of inheritance. I think it points out, too, the need for more clincs of this sort over the country, so that people can really get what is sometimes comforting and sometimes disturbing advice and information.

CHAIRMAN BUGHER: That's a very useful comment.

I suspect that the matter of a team as against a single individual trying to carry the advisory function could be debated, probably, most of the day, so I am not going to encourage anything of that kind. We will have occasion, I hope, at various times during the day, when we are meeting informally, to explore some of these things more or less directly.

May we turn from things of the type that Dr. Warkany has been discussing, which have been expressed in morphologic terms to a very substantial extent, to an area which is highly functional in its substance, and oftentimes less immediately tangible, the general area of psychic functions. Our next paper is "Genetics in Psychiatric Practice," by Dr. Whittier, who is presently Director of the Creedmor Institute for Psychiatric Studies.

GENETICS IN PSYCHIATRIC PRACTICE

JOHN R. WHITTIER, M.D.
Creedmoor State Hospital
and Institute for
Psychobiologic Studies

BLEULER WROTE IN 1911 THAT HE UNFORTUnately "could not shirk the uncomfortable duty of coining a new name" for the disease he then called "schizophrenia." Definition of the terms in this paper is an uncomfortable but equally demanding duty. Since I speak as a neurologist and psychiatrist before a group largely composed of geneticists, I will claim naïveté, take some risks, and proceed to discharge my duty.

It is often possible to find in lay writings the simplicity, directness, and meaning which medical writings sometime obscure in their magnificent and specialized terms. For this reason I will occasionally resort to Webster's Dictionary (22).

With the aid of helpful definitions I will consider (1) etiological concepts in psychiatry, (2) operational characteristics of medical psychiatric practice, and (3) genetics as a tool in these operations.

It is not generally recognized that all mental disorders have been divided into two major groups for psychiatrists (4). These groups are mental disorders characterized by diffuse impairment of brain tissue and mental disorders characterized by difficulty in adaptation. These two major groups are subdivided into three categories: (1) diseases caused by or associated with the impairment of brain tissue function, which may by acute or chronic, (2) mental deficiency, (3) disorders of psychogenic origin without clearly defined physical cause or structural change in the brain. The last is practically synonymous with the second group—mental disorders characterized by difficulty in adaptation. For medical purposes the "Standard Nomenclature of Diseases and Operations" classifies all these mental disorders under "Diseases of the Psychobiologic Unit" (pp. 85-92). These disorders, then, are those for which a concept of etiology must be adequate.

Only two years ago the National Advisory Mental Health Council reported that "the concept of etiology as embraced by modern psychiatry differs from the simple cause and effect system of traditional medicine. It subscribes to a "field theory hypothesis" in which the interactions and transactions of multiple factors eventuate in degrees of health or sickness. This concept, although still not fully appreciated in psychiatric diagnosis or treatment today, was not new even then. Two years prior, Ewen Cameron (3) described to an annual meeting of the American Psychopathological Association how the concept of causality, including multiple causation, had taken the place of specific cause and was giving way to the idea of event sequence as "long chains of events passing forward and continually being modified by interplay with each other." Adolph Meyer, Cameron noted, had preceded him by 50 years, fighting for this concept of "multiple etiologic bases."

Textbooks and periodical literature on mental disorder characteristically refer to "factors," "components," "contributions," or "aspects" in any consideration of etiology. These references can be grouped into categories which may be termed *genetic, experiential,* and *circumstantial* (23). These terms often appear explicitly, and equally as often are tied together by terms of "interaction" or "transaction," but it may be rewarding to consider each of them in some detail.

"Genetic" is the adjective which denotes the genes and their influence manifested

as potential, or genotype, and expression, or phenotype. There is an unfortunate use of this adjective in dissimilar ways by the disciplines of genetics and of psychiatry. Maurice Levine has written: "In psychiatry the term 'genetic diagnosis' refers to the totality of those forces involved in the genesis and origin of current forces. Such genetic forces are hereditary or constitutional in small part but are predominantly a matter of early life experience and individual reaction" (13). In the concept being developed here, the term genetic refers to genes as specific factors contributing to mental disorder.

It has been clearly demonstrated that genes, and the behavior of the material of which they are composed and by which they are expressed, determine morphology and function of cells, tissues, organs, and the integration of these not only in an absolute sense, as in the case of Huntington's disease, but in a conditional manner depending upon the experiences and circumstances unique to the individual, as in some forms of schizophrenia.

The term "experiential" has had a general utility for many decades in psychological and psychiatric literature. From the Latin *experientia* (*experire* "to try") the noun "experience" is given prescient definition by Webster as "The actual living through an event or events; actual enjoyment or suffering; hence, the effect upon the judgment or feelings produced by personal and direct impressions." The adjective "experiential" appropriately applies to the many operations of sensation, percept and concept formation, during the interactions and transactions between the organisms and environment which characterize survival. These operations include the broad subjects of intellection, hedonics, learning, motivation, and defense formation.

Our third and final etiological term is derived from the noun "circumstance," provided by Webster for us as "one of the conditions under which an event takes place or with respect to which a fact is determined." Clearly, a condition or circumstance may be within the organism or in its environment, and it may occur intermittently, once, or continuously, with varying strength. It now becomes apparent that experience becomes specific for the organism in the circumstances provided during survival. The term genetic can now be observed to pertain to the duration of the pedigree far exceeding the lifetime of the organism. The adjective experiential, depending as it does upon some degree of organized sensation and perception, applies properly to the period from birth to death, perhaps including the last two trimesters of pregnancy. The adjective circumstantial properly refers to the period from conception to death, as it has been well demonstrated that a variety of intra-uterine events may determine form and function of the embryo.

It is interesting to note that the diagnostic and statistical manual of mental disorders of the American Psychiatric Association approximates this triplicate formulation of "elements" or "factors" determining behavior (Complementary Diagnostic Evaluation, pp. 46-69). It is specified to consist of the elements (1) external precipitating stress (our circumstantial adjective), (2) premorbid personality and predisposition (our genetic and experiential adjectives taken together), (3) the degree of psychiatric impairment, with which we are not presently concerned.

It is not enough, however, to provide oneself with descriptive adjectives. Some formulation of the way in which they relate to one another must be provided. For the individual organism the phenomena determined by genes, experience, and circumstance are "liable but not certain to occur." Description of the status of an organism, and indeed its related evaluation as adapted or maladapted with respect to probability of healthy or unhealthy survival, is *contingent* upon a giving or supplying of each of the attributes or characteristics in com-

mon with more or less of the other two. One can then view Cameron's "event sequences" and the evaluation of adaptation or maladaptation at any time as contingent upon factors of genetic, experiential, and circumstantial classes. For the human organism this is implicit in the operation of diagnosis.

We have now completed a presentation of an etiology general enough to include medical disorder, yet specific and flexible enough to merit application in the field of psychiatry.

Provided with this concept of factors having genetic, experiential, and circumstantial characteristics, let us proceed to a brief survey of the operational characistics of present psychiatric practice, paying special attention to diagnosis.

It has long been a melancholy observation of teachers of medicine that, when the well-rounded, multi-disciplined, group-clinic oriented medical student completes his internship and elects psychiatry as his field, he is promptly seized with amnesia for medical diagnostic process, views behavior from the point of a Freudian splinter school, and relies upon history emerging from unstructured sessions over a period of many months. Or at the other extreme he assists his patients to select the tranquilizer they require during a period of more or less double-blind experimental trial, with a multiple crossover design feature. Psychiatric diagnosis, however, is no more dependent upon a single segment of the individual or upon response to treatment than is diagnosis in any field of medicine. It is still a process by which a more or less systematic description is undertaken in collaboration between the physician and the patient or informants in order to arrive at an understanding of the sources of the phenomena presented. Traditionally this systematic review has included the present illness, a system review, a personal history including developmental, medical and educational data, and a family history.

Upon completion of the medical history, diagnosis in psychiatry, as in medicine, proceeds to physical and neurological examinations if these studies have not been properly completed before. The psychiatrist may be led by information developed during these operations to recommend additional specific special tests or laboratory examinations, including psychological testing, X-rays, and clinical laboratory tests of routine or special nature. At each step in this process the psychiatrist may and should make observations about genetic factors, especially in the detailing of family history. In psychiatric practice the greatest usefulness of genetics is in diagnosis and prevention, although I will comment on its use in communication during treatment and management. It is probable that genetics has greatest application in the early periods of mental disorder. Here symptoms may be minimal or even absent. Here maximum therapeutic effects may be obtained. Early control over experience and circumstance may be sufficient to minimize genetic factors otherwise disastrous to patient or family.

It should be understood that a diagnosis, or a working differential diagnosis, is formed in the minds of one or more people, and its meaning varies with the characteristics of the person. The first person to reach a diagnosis is usually the psychiatrist, although there are rare and startling instances where intelligent patients reach a correct diagnosis with the aid of several senses and facilities of the public library. To the psychiatrist a diagnosis indicates (1) confirmatory tests or studies, (2) treatment and management measures, (3) communication to persons intimately concerned, (4) continued observation. Persons concerned include the patient, the patient's relatives, attending physicians, welfare agencies, and laboratories for special studies.

The significance of the formation and communication of diagnosis is that it is selective, privileged and confidential, and diagnosis is often indefinite in early stages

of disorder. As is the case in medicine for any disease, it becomes a matter of clinical judgment *to whom, how much, in what terms,* and *when* diagnosis of psychiatric disorder and its significance is communicated. Several general principles apply. Sufficient information must be communicated to the patient, or responsible relatives, to guard the physician against charges of malpractice by negligence. The information required is usually that sufficient to aid the responsible family group to guide their actions, as is the case in medicine generally. There are few psychiatric disorders of such unmitigated hopelessness that the psychiatrist need hesitate to communicate the facts, provided his own hostility to a largely genetic disorder, having a minimal experiential or circumstantial component, is not displaced. Genetic education in psychiatric practice often must teach the patient to live with possibilities and uncertainties.

We may turn to specific psychiatric disorders and consider the operation of diagnosis further, together with some attention to treatment and prevention. Among the chronic brain syndromes Huntington's disease is unique. It is a degenerative disorder without parallel, in which the genetic factor is defined by a relatively simple dominant mode of transmission, one-half of all offspring carrying the gene, with affected persons certain to transmit the disorder to one-half of their children. Although abnormal movements may be its only symptom, its later picture of psychosis combined with hyperkinesia is scarcely to be confused with any disorder other than so-called "senile chorea." An adequate family history is definitive provided it can be obtained. Again, it is in the early stages of this disease that knowledge of the heavy genetic factor guides psychiatric treatment and management. Understanding the significance of the contingency concept provides excellent reassurance for treatment of the patient with the maximum experiential and circumstantial tools available. The analytically-oriented psychiatrist knows that he misses much of the material and influence available to his profession if he does not explore attitudes toward information before he provides it in patients and relatives. He can often prepare a patient for genetic information which otherwise would occasion new and emergency circumstances. He can protect patients from including genetic influences among the expressions of hostility, or among guilty fears. These operations are those in which a psychiatrist has unique experience, and which he can contribute in training settings to geneticists, psychologists, social service workers, and others who might benefit.

Additionally, psychiatrists may anticipate a new and challenging field in the prevention of mental disorder with a large genetic component, which may be termed perhaps "psychotherapeutic sterilization." This need not deprive pre-marital or marital pairs from planning parenthood but should aid them to consider adoption or artificial insemination as acceptable ways of achieving it.

Pick's and Alzheimer's diseases are psychoses in the pre-senile period and have less well-defined genetic factors, but Jervis (9) reviewing these disorders concluded (p. 283) that "cases are known in which genetic factors play the dominant role in determining the pathologic process. The possibility of familial occurrences may be considered, indeed, a common characteristic of pre-senile dementias." Grünthal and Wenger (7) have given detailed consideration to the genetic factor in Alzheimer's disease, and Löken and Cyvin have described Alzheimer's changes in siblings (14).

Huntington's disease and the pre-senile psychoses are rare. There are two chronic brain syndromes, however, which contribute significantly to the thousands of patients admitted to state hospitals at age 60 and over. They are generally termed "psychosis with senility" and "psychosis with cerebral arteriosclerosis." Our knowledge of the relative weight of the determinants,

their definition, recognition, and control is still almost formless. Treatment and management are subject to the same considerations offered for Huntington's disease.

Prevention, however, and indirectly diagnosis, are in extremely interesting phases. Many studies are in progress, especially of experiential and circumstantial factors, not appropriate to detail here. Kallmann concluded from data reported in 1951 that the "occurrence of either (senile or involutional psychosis) not only presupposes the capacity for survival beyond the beginning of the involutional period and the ability to live through the preceding years of maturity without succumbing to any other kind of psychosis but also requires a combination of etiological components, which individually would not be sufficient to produce a psychotic reaction syndrome." Kallmann's recognition of status contingent upon contributing factors was explicit. In the 1956 paper he writes of "interacting causative elements."

Psychiatrists are still feeling their way, with the help of the biochemists and anthropologists as well as geneticists, among the interaction of factors in general and in cerebral arteriosclerosis which contribute so heavily to psychoses of the senium. The genetic factor cannot be overlooked. It has been shown, for example (6), that the Navajo Indian's freedom from atherosclerosis is independent of diet. A further singular and promising lead toward genetic factors in atherosclerosis, now under investigation in the research unit at Creedmoor, appears as the disease progeria, characterized by atherosclerosis and senility in the first decade, and recently described in two sisters (15). It is hard to quarrel with an assertion that genetic studies, especially in collaboration with other disciplines, offer much promise for the prevention of mental disorders of the senium.

Manic-depressive reaction provides another special instance of psychiatric diagnosis aided by genetics. Adequate family history will usually differentiate these patients from psychotic reactive depressions, involutional psychosis, or schizo-affective disorders, although the genetic mechanism is considered by Kallmann and others to be by irregular dominance. The psychiatrist who considers a young depressed male will tend to reach an especially guarded opinion, and tighten management and treatment, if his knowledge includes cyclic hyperactivity succeeded by suicidal attempts in the patient's father or occasionally in the grandparents or collateral [illegible]es.

Many schizophrenic reactions are now recognized to have genetic components. Drs. Kallmann (10) and Lauretta Bender (1) have done much to further this recognition. The need now is for better clinical definition and for detailed analysis of the three factors. The psychiatrist is not diagnosing or treating adult or juvenile schizophrenia intelligently unless he is aware of the interaction of genetic, experiential, and circumstantial factors in this disorder. Kallmann (12) recently formulated his concept of juvenile schizophrenia to include the factors of (1) gene-specific vulnerability to stress arising from ordinary environmental circumstances, (2) an apparently non-specific impairment in the organization of these normal protective functions which bestow on many persons a relatively high degree of resistance to an unfavorable environment.

In the Creedmoor unit a recent study, apparently one of the first of its nature (17), compared parents of normal children with parents of schizophrenic children by a battery of psychological tests and found differences in personality between these parental groups. It is probable these differences were of a nature not deriving simply from the circumstances and experiences of being parents to schizophrenic children, but that conclusion must wait upon other studies. I will make subsequent reference to gene-determined personality characteristics.

Prevention of the schizophrenic reaction

is as challenging to the fields of genetics and psychiatry as is prevention of Huntington's disease. It seems pertinent to raise here the possibility, presently ignored in the excitement and therapeutic promise of the tranquillizers, that if the fertility differential usually characterizing schizophrenic reactions is reduced, these medications may ultimately increase the incidence of the disorder. It is not too early to pay attention to this possibility and to benefit by whatever can be learned from experiences with diabetes, idiopathic epilepsy, and other diseases with genetic determinants similarly controlled in part by medication.

Finally, we may consider the psychoneurotic disorders. Here genetics still has little to offer the practicing psychiatrist. Much is waiting, however, upon developments specifying early behavior patterns, and definitions of stability and individuality of defense-mechanisms. The significance of strain-differences within species is beginning to be related to behavior (19) and to response to drugs (8). It is patent that an organism characterized by a low level of spontaneous activity would have less probability of conflict in restrictive parental or cultural circumstances than one set at a high level.

Additionally, it seems quite probable that in the human, psychological defense mechanisms are selected for the individual by the genes and either made available under biochemical or interpersonal emergencies, or subjected to disorganization, contingent upon circumstances and experience.

It is inevitable that the practicing psychiatrist, having begun to be at some peace with psychoanalytic concepts, and being recently disturbed by biochemical concepts, must prepare himself for additional pressures from genetics. That he is willing to bear this additional pressure is indicated by responses to a questionnaire recently sent to the professional staff at Creedmoor State Hospital, asking whether they would consider useful a Genetics Laboratory proposed for consultation and for counseling of relatives. One respondent abstained, one was negative, and 26 were affirmative. Such a nearly unanimous favorable response in the field of psychiatry should be comforting to geneticists, whose lights, beginning with Mendel's, have often been long hidden.

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Chairman Bugher: I think the degree of unanimity among the psychiatrists you mention would be an unsual phenomenon with respect to any subject.

One of the very significant things that Dr. Whittier has called to our attention is the ever-present booby trap of semantics which exists in any multidisciplinary approach, where a given symbol or word turns out to mean widely different things to different people, without their always being conscious of the fact. It is very helpful to have this brought out so clearly.

We can move on into a field which is again morphological but one which is especially attractive to the geneticist who is working with facial structures, and all these aspects of development. To speak on "Genetics and Dentistry," we have Dr. Carl Witkop, who has for a considerable period of time devoted his attention to problems of this kind in the National Institute of Dental Research in Bethesda.

GENETICS AND DENTISTRY

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The dentist is concerned with three major problems relating to genetics. The first problem concerns the safe use of diagnostic X-rays to minimize any germinal or somatic cell damage. The second problem deals with those inherited factors influencing the normal growth and development of oral structures. The third problem concerns the inherited diseases of the teeth and surrounding structures. It is this last problem that is of interest to the heredity counselors.

In some dental diseases inherited factors can be decisive or only contributory to the production of a specific illness. For example, *dentinogenesis imperfecta,* an inherited defect in the formation of dentin, is produced only when a person is heterozy-

gous for the defective gene. However, variations in the clinical appearance in these teeth are partially ascribable to environmental factors to which these defective teeth are subjected after eruption into the oral cavity. On the other hand, the work of Hunt (2) on dental caries in rats indicates that hereditary factors such as anatomical variations in tooth form (5) affect the caries susceptibility but that environmental factors are most likely the major etiological agents in this disease (3). It is only in the former instance, where the disease is primarily genetically determined, that the heredity counselor can make relatively accurate predictions at this time.

Inherited Dental Diseases

The intrinsic diseases of dental significance can affect oral structures only, or they can be present as oral manifestations of generalized hereditary disease. Table 1 illustrates these defects. Only those conditions that have been fairly well established as genetic in origin have been included. It is to be remembered that some of these diseases may be mimicked by non-genetic phenocopies. A few of these defects will be discussed in detail.

Heritable Defects in Dentition Without Generalized Defects

In order to determine the prevalence, inheritance and classification of hereditary enamel and dentin defects, a survey of 96,471 children was conducted in the State of Michigan (15). There are at least five distinct inherited defects in enamel. All teeth in both dentitions are affected except in local hypoplasia. Extensive clinical studies at the National Institutes of Health failed to reveal any other consistent physical or metabolic abnormality in patients affected with these conditions. All inherited enamel defects taken together occurred once in 14,000 to 16,000 children.

1. *Hypoplaisa of Enamel*

The enamel is about one-fourth the thickness of normal enamel, has a granular surface, and is very hard. The teeth are light brown in color and are usually separated at the contact points. Schulze (11) reported that this condition is inherited as a sex-linked dominant in five extensive pedigrees.

2. *Hypocalcification of Enamel*

This condition is the one commonly referred to as *amelogenesis imperfecta* (13). The enamel is dull brown in color and very soft with a rough surface. It can be scraped from the underlying normal dentin by a sharp instrument. The enamel persists only a short time after the teeth erupt. This condition is inherited as an autosomal dominant trait.

3. *Hypomaturation of Enamel*

In this condition the teeth are an opaque white when they first erupt, but they turn light brown later. Calcium salts are deposited in the matrix but do not mature to the hard apatite crystal. The tip of an explorer can be forced into the surface of the teeth with firm pressure. A collar of normal-appearing enamel may be present at the cervical portion of the crown. This condition is transmitted as a sex-linked recessive trait.

4. *Pigmented Hypomaturation of Enamel*

The enamel is of normal thickness but is not so hard as normal enamel. The surface is shiny, agar brown in color, with a brown pigment extending throughout the thickness of the enamel. Histochemical stains indicate that this is not blood pigment. This condition is probably inherited as an autosomal recessive trait.

5. *Local Hypoplasia of Enamel*

Only the primary teeth may be affected in this condition. Brown pitted or lined hypoplastic areas occur mostly on the incisors and premolar teeth. All teeth may show hypoplasia. There is wide variation in the number of teeth affected in individuals from the same kindred. In two instances the trait was transmitted by persons with normal-appearing teeth, once by a male and once by a female. This is inherited as an autosomal dominant trait.

In addition to these five conditions there are probably at least two more enamel de-

TABLE 1.
HEREDITARY ORAL DISEASES

Oral Disease	MODE OF INHERITANCE *D* = Dominant *R* = Recessive *S* = Sex-linked *IS* = Intermediate sex-linked	ACCURACY OF GENETIC PROGNOSIS ••• = accurate •• = approximate • = questionable
HERITABLE DEFECTS IN DENTITION WITHOUT GENERALIZED DEFECTS		
Hypoplasia of Enamel	*SD*	••
Hypocalcification of Enamel	*D*	•••
Hypomaturation of Enamel	*SR*	•••
Pigmented Hypomaturation of Enamel	*R*	•
Local Hypoplasia of Enamel	*D* (with incomp. penetrance)	••
Dentin Dysplasia	*D*	•••
Dentinogenesis Imperfecta	*D*	•••
Missing or Peg Laterals	*D*	•••
Missing Maxillary Incisors & Cuspids	*D* or *R*	••
Missing Premolars	*D*	••
Missing Third Molars	*D*	••
Gigantism of Maxillary Central Incisors	*D*	••
Fused Primary Mandibular Incisors	*D*?	•••
Familial Dentigerous Cysts	*D*	••
HERITABLE DEFECTS IN DENTITION WITH GENERALIZED DEFECTS		
Dentinogenesis Imperfecta with Osteogenesis Imperfecta	*D*	••
Enamel Hypoplasia in Vitamin D Resistant Rickets	*D* (irregularly)	••
Enamel Hypoplasia with Epidermolysis Bullosa Dystrophia	*R*	••
Local Hypoplasia of Enamel with Fanconi Syndrome	*R*?	•
Missing Teeth with Ectodermal Dysplasia	*IS* or *D*	••
Missing Premolars with Premature Whitening of Hair	*D*	•••
Missing Lateral Incisors with Ptosis of Eyelid	*D*	••
Retarded Eruption with Cleido-Cranial Dysostosis	*D*	••
HERITABLE DEFECTS OF ORAL STRUCTURES WITHOUT GENERALIZED DEFECTS		
Ankyloglossia	*D*	••
Elephantiasis Gingivae	*D*	••
Harelip and Harelip with Cleft Palate	*R*?	•
HERITABLE DEFECTS OF ORAL STRUCTURES WITH GENERALIZED DISEASES		
Gangrenous Stomatitis with Acatalasemia	*R*	••
Periodontis with Agammaglobulinemia	*SR*	••
Periodontitis and Osteoporosis of Jaw Bones with Thalassemia Major	*R*	•••
Alveolar Bone Changes in Sickle Cell Disease	*R*	•••
Gingival and Postoperative Hemorrhage in Hemophilia and Christmas Disease	*SR*	•••
Mucosal Telangiectasia in Hemorrhagic Telangiectasia (Olser)	*D*	••
Facial Angiomatosis with Sturge-Weber's Disease	*D* (irregular)	•
Oral Hematomas with Ehlers-Danlos Syndrome	*D*	••
Facial Deformity in Gargoylism	*R* (*RS*)	••
Facial Deformity with Mandibulo-Facial Dysostosis (Franceschetti)	*D* (irregular)	••
Facial Deformity with Cranio-Facial Dysostosis (Crouzon)	*D* (irregular)	••
Micrognathia with Pierre Robin Syndrome	*R* (incomp. dom.)	•
Hypoplasia of Maxilla with Achondroplasia	*D*	••
Multilocular Cystic Fibrous Dysplasia of the Jaws and Face (Jones)	*D*	•••
Osteosclerosis in Albers-Schönberg Disease	*D* (irregular)	••
Hyperostosis of Jaws in Generalized Hyperostotic Bone Disease (Witkop)	*R*	•••
Hypercementosis and Bone Changes in Osteitis Deformans (Paget)	*D* (incomp.)	•
Neurofibroma and Pigmentation in Neurofibromatosis (von Recklinghausen)	*D*	••
Circum-Oral Pigmentation with Gastrointestinal Polyposis (Peutz-Jegher)	*D*	••
Facial Pigmentation and Carcinomas of Lip in Xeroderma Pigmentosum	*ISR* or *R*	••
Gingival and Lingual Amyloid Deposits in Familial Amyloidosis	*D*	••
White Spongy Nevus of Mucous Membranes	*D*	•••

fects that are hereditary in nature. We have investigated reports that dentists in a community see what is at first called fluorosis after 1 ppm of sodium fluoride is added to the water supply. On examining these children, we find as high as 15 per cent of them have some variation in the color of the teeth—usually a yellow. This is not fluorosis. One explanation may be that there are several forms of genetically controlled normal variants of enamel similar to the variants of hemoglobin. This would offer a possible explanation for the inconsistent results obtained in many attempts to determine the chemical and structural composition of enamel, and in turn account for the differences in D M F[1] rates seen in members of the same family subjected to similar environmental influences.

Two hereditary defects of dentin were found in the survey: *dentin dysplasia* and *dentogenesis imperfecta.*

Dentin dysplasia is also known as rootless teeth. It is frequently misdiagnosed as *dentinogenesis imperfecta* (9). The crowns are well formed and normal in color. The roots may be absent, blunted or may be only short spicules. A characteristic chevron or half-moon-shaped remnant of pulp chamber is seen in the X-ray of these teeth. Root canals are usually absent. Many teeth show large radiolucent areas around the apices of the root. The condition is transmitted as an autosomal dominant trait.

Dentinogenesis inperfecta has been called opalescent dentin, Capdepont's teeth, *odontogenesis imperfecta,* hereditary brown teeth, and shell teeth. Many of these names originated because one or two of the many variations this condition shows were emphasized by the author as points of differential diagnosis. We have seen some 350 cases of this condition in extensive kindreds. We also have examined as many as 140 affected individuals in the same kindred and have seen all the variations ascribed to separate entities.

[1]Decayed, Missing and Filled—a standard of dental caries experience.

Dentinogenesis imperfecta occurs in the general population of Michigan about once in 8,000 individuals. In certain isolated populations the frequency is much higher (14). The teeth vary from an opalescent blue to an amber brown in color. The enamel may fracture from the defective dentin soon after eruption or may remain intact on the crowns of the teeth throughout life. The enamel may be normal or hypoplastic. The crowns are usually bulbous in shape and the roots short. The pulp chambers are usually absent, but may be normal in size or even very large, resulting in a shell tooth (8, 14). This condition is transmitted as an autosomal dominant trait with nearly complete penetrance.

The homozygous state for this condition was not seen, but in one marriage where both parents were affected the mother had seven pregnancies with only two viable offspring. Both children appeared to be heterozygous for this condition. The other five pregnancies terminated in abortions between the second and fifth month of gestation. The homozygous state of these genes may be lethal. Linkage studies were carried out between *dentinogenesis imperfecta* and phenylthiocarbamide taste testing and secretor factor in saliva. In general, the same sibships were used for both the saliva and the taste testing. The results of the paired-sib analysis are presented in Table 2. It appears that there is probably linkage between *dentinogenesis imperfecta* and phenylthiocarbamide taste trait.

TABLE 2.
LINKAGE DATA

PAIRED SIB METHOD				
Dentinogenesis Imperfecta—PTC				
LL	LU	UL	UU	Total
28	13	10	24	75
$x^2 = 11.24$		$df = 1$	$P < .001$	
Dentinogenesis Imperfecta—Secretor Factor				
LL	LU	UL	UU	Total
19	19	11	11	60
$x^2 = 0$				

Congenitally hereditary missing teeth may show some variation in the number of teeth missing depending on whether the person is heterozygous or homozygous for the gene involved (4). Some of these genes are relatively common in the population. Grahnen (1) reported prevalence of 5 to 6 per cent of missing teeth, excluding third molars, in Swedish populations.

Heritable Defects in Dentition With Generalized Defects

Dentinogenesis imperfecta sometimes occurs as part of the *osteogenesis imperfecta* syndrome (12). *Dentinogenesis imperfecta* may also occur as an independent hereditary trait as does blue sclerae and otosclerosis—the other manifestations of the fragile bone disease. *Dentinogenesis imperfecta* is found in familial cases of *osteogenesis imperfecta* and also in those apparently sporadic cases in which no affected predecessor can be detected. In several kindreds the tooth defect has proved to be a more reliable indication of affected individuals than blue sclerae. In one such kindred the blue sclerae were absent, but the dominant inheritance of the trait could be traced through the members with defective teeth for three generations. The combination of fragile bones, *dentinogenesis imperfecta* and blue sclerae then appeared in our propositus and three first cousins.

It is not known whether *dentinogenesis imperfecta*, occurring as a separate entity, and *dentinogenesis imperfecta* with *osteogenesis imperfecta* are exactly the same condition (9). Schulze (11) claims that there are microscopic differences. However, there are a great number of similarities between these two conditions. There are also similarities between the tooth defect and the bone defect.

McKusick (6) states that there is a bell-shaped curve of severity of *osteogenesis imperfecta* and that the separation of the congenita and tarda forms is somewhat artificial as both forms may occur in the same family. A like situation exists for *dentinogenesis imperfecta*, both with and without bone disease, so that both severe and mild forms of tooth defect may occur in the same kindred. In our cases the teeth erupt early in the more severely affected individuals. However, Pindborg (7) reports delayed eruption of the teeth. We have seen the eruption of permanent teeth as early as three years of age. There is another similarity to the congenita and tarda types of bone defect in that the teeth which erupt first are the most severely affected. The primary teeth, permanent first molars and incisors are usually very defective. The permanent cuspids and second molars, which erupt at 11 and 12 years of age, are less severely affected. There is apparently a tendency toward normal dentin formation in the teeth that develop later. The cuspid and second molar begin their development at about 2 to 3 years of age; therefore, the lessened severity of the defect in these teeth cannot be ascribed to hormonal changes in puberty.

In sections of bone from cases of *osteogenesis imperfecta* there is found a basophilic, PAS positive substance not present in normal bone (6). A similar substance is found in teeth affected with *dentinogenesis imperfecta* with or without *osteogenesis imperfecta*.

Ectodermal dysplasia is a condition in which the ectoderma portions of the tooth germs fail to develop properly, resulting in absence of all or some of the teeth. Males are more severely affected than females. This condition is classified as an intermediate sex-linked trait, because females who carry this gene usually show absence of at least one or two teeth or other stigmata of this disease (10).

Heritable Defects of Oral Structures Without Generalized Defects

Ankyloglossia or tongue-tie appears to be dominantly inherited. We have been studying this condition and its effects on speech in a population residing in Southern Maryland. We found during our den-

tal and medical studies that 50 people of the 731 examined had a prominent lingual frenum that prevented them from raising the tip of the tongue beyond a point midway between the upper and lower incisor teeth when the mouth was opened to its fullest extent. The mode of inheritance of this condition is difficult to determine in most families, because in many new-born infants the frenum is cut, if it appears to interfere with tongue function.

Heritable Defects of Oral Structures With Generalized Defects

The Ehlers-Danlos syndrome is of particular interest to dentists because of the frequency with which these patients have post-operative complications of massive edema and swelling. This condition has been neglected in the dental literature, and very few descriptions and reports of this disease appear anywhere (6). Yet, it is perhaps one of the most common connective tissue diseases encountered in Southern Maryland among a group selected as a control for our inbred population studies. Biochemical studies on these patients have failed to reveal any defect in hydroxyproline metabolism.

White spongy nevus of mucous membranes is of dental interest because it is sometimes misdiagnosed as precancerous leukoplakia. It has frequently been described as an oral lesion only but usually involves vaginal mucosa also (16).

A Research Program in Hereditary Diseases

In 1955, we examined three individuals with *dentinogenesis imperfecta* who claimed vague relationship with one another. In trying to determine the exact relationship by kindred chartings, it soon became apparent that we were dealing with a most unusual family. In tracing all sides of all affected sibships, we found that only eight surnames appeared which were repeated with monotonous frequency. Other defects of a hereditary nature were found in these families which included an ear defect, albinism, polycystic kidneys, deaf-mutism and Brailsford-Marquio's disease. Further investigation disclosed that we were dealing with a population isolate. This isolate comprises about 5,000 individuals of mixed racial ancestry who did not consider themselves Negro and were not admitted into the white marriage patterns of the community. We are now conducting extensive research on the social, medical, and dental aspects of this group. Because the in-marriage pattern has persisted in this population since before 1760, many recessive characteristics appear in the homozygous state. For example, 55 albinos have appeared in this population; 48 are living today. Seven hundred and thirty-one unselected individuals were examined this summer. Of this number 104 had positive sickling tests, including both SA and SS hemoglobin patterns. A rare peculiar form of recessive generalized hyperostotic bone disease was found in five members of one sibship. This disease has probably not been described before. All bones are affected. The first symptoms appear at about 4 to 5 years of age with a swelling, always on the right side of the jaw, accompanied by a seventh nerve paralysis which persists after the swelling subsides. Gradually both sides of the face are involved. Loss of hearing begins at about 6 to 9 years of age, and becomes progressively worse. A progressive retinal atrophy and exophthalmos develops. The base of the skull is involved in the hyperostotic process early, and eventually the jaws and facial bones show the hyperostotic changes of *leontiasis ossea*. The long bones show tremendous cortical thickening. They are considerably larger than normal but retain their normal configuration. The usual laboratory tests are within normal limits. There are no hematological changes. There is no history of fractures in these cases.

This population offers the opportunity to find matings rare in human material. In

diseases where the genetic factors are only contributory, it may be possible to further define the role heredity plays in their etiology. For example, after examining the dental condition of 780 patients, it was determined that the D M F rates and the lactobacillus counts[2] were similar to those in communities with 1 ppm of sodium fluoride in the water supply. In the communities with fluoride in the water supply these rates are about 60 per cent lower than communities without fluoride. In Prince Georges and Charles Counties, Maryland, where this isolate resides, the fluoride content varied from .02 ppm to .08 ppm—far below that required to produce a decrease in caries activity.

[2] A bacterial test of dental caries activity.

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DISCUSSION

Chairman Bugher: I think we all appreciate the wealth of material which is available in the dental clinic. The accumulation of such data is an important function of the human geneticist.

I was curious myself about one thing, because you brought up the question of the lethality of the homozygous condition. I think that's the first mention of this problem. Are there others of these dental disturbances that have a similar feature?

Dr. Witkop: We don't know because these traits are so uncommon in the population that a mating which would give you a homozygous offspring would be extremely rare. It was only in an isolated population, where people were forced by social and religious factors to marry within their own kind, that a situation like this did turn up with any frequency.

Two such marriages have occurred where both parents have *dentinogenesis imperfecta.* One was in past generations where we cannot obtain good data on the mothers' pregnancies, but in this particular instance, where we do have information, the woman had been examined repeatedly after each miscarriage. These examinations did not reveal a specific cause of the miscarriages. Unfortunately none of the fetuses were examined microscopically.

QUESTION: Has the new syndrome been given a name?

DR. WITKOP: We are calling it recessive generalized hyperostotic bone disease.

QUESTION: Would Dr. Witkop care to comment on the counseling aspects of this?

DR. WITKOP: I think Mrs. Dyson in the following paper will probably answer some of those questions. Certainly the health authorities in the County are concerned about the children needing glasses because of albinism, nystagmus and eye trouble.

The Howard Dental School has been repairing all the cases of *dentogenesis imperfecta*. They either extract the teeth and put in a denture, or else they crown the teeth which is a very expensive procedure.

DR. MAX LEVITAN: Are these conditions generally well known enough so that students in dental schools learn about them?

DR. WITKOP: In general, no. They usually learn about *dentogenesis imperfecta*, but this condition is confused in the dental literature with *dentin dysplasia*. As you can see, the two conditions that we differentiated here have certain similarities. Both lack root canals and pulp chambers. In fact the last two cases reported in the *Journal of the American Dental Association* were called *dentogenesis imperfecta* but were actually *dentin dysplasia*. These two conditions are entirely separate entities.

DR. BENTLEY GLASS: Most of these defects you have discussed are of the grosser type. I would like to ask if you also find an equal wealth of hereditary conditions that relate to the spacing of the teeth and the shapes of particular teeth, the things that the anthropologists are interested in.

DR. WITKOP: Yes. My objection to most studies on physical anthropology is they show that a trait is prevalent in a population and then say it must be heredity. I'm old-fashioned on these things. I'd like to have the families studied also.

However, there are differences in tooth form. Shovel-shaped incisors and large maxillary incisors, which seem to be inherited as a dominant trait, have been shown to be genetically determined.

DR. ALLEN: Dr. Warkany has very impressively demonstrated the value of accurate diagnosis in family counseling. I believe that many of these conditions are so difficult to diagnose and so rare that the ordinary practicing dentist cannot be relied upon to give a differential diagnosis. In these situations I suspect that the counselor can neither resort to the aids that have been provided us nor to the risk figures but must study the family.

DR. WITKOP: That would be the best advice to give: to look and see how it is inherited in a family, and then make your prediction on that basis.

Two or three of these conditions are fairly well known and can be accurately diagnosed by an oral pathologist, but to differentiate among some of them is very difficult. As a general rule of thumb, if both dentitions are affected, it's usually genetically determined. I have seen conditions where this was not so, but the only thing I can say is that most dentists do not know what these conditions are. They usually attribute these defects to a fever in childhood or to some other sort of infectious disease occurring in the early period of life. Fevers and severe vitamin deficiencies early in life do cause defects that look similar to local hypoplasia, but there is nothing I have ever seen that causes *dentin dysplasia*, hypocalcification, or *dentogenesis imperfecta*, or hypoplasia of enamel where the enamel is very thin, that was other than a genetic defect.

CHAIRMAN BUGHER: How broad our field of concern is, when you consider the variety of the scientific disciplines which are represented here today! Certainly, the public health nurse has been one on whom the public at large —parents, in particular—have relied and do rely with increasing frequency for sound advice and guidance in many fields, not the least of which is to assist with the genetic problem the family may be confronting. To discuss "Genetics in Public Health Nursing," we have Mrs. Hazel Dyson, who is not only a registered nurse but has a special interest in the field of dental research at the National Institute.

GENETICS IN PUBLIC HEALTH NURSING

HAZEL R. DYSON, R.N.
CARL J. WITKOP, JR. D.D.S.
SHIRLEY S. BUTTERS, R.N.
National Institute of Dental Research
National Institutes of Health
Public Health Service
Department of Health, Education,
and Welfare

THE FUNCTIONS OF THE PUBLIC HEALTH NURSE have been defined in many ways. At a recent meeting of the American Public Health Association much time was devoted to the discussion of recent trends in public health thinking (McKeever, *et al.*, 1956) and the role to be played by the nurse in the solution of the health problems now confronting us (Leavell, 1956). Intrinsic disease is assuming more importance in these problems as at least two per cent of the general population has serious genetic illness (Neel, 1956). Fleck (1956), in defining the duties of public health nurses, states, "They function as the eyes and ears of all health services," and are in "a strategic position to collect epidemiologic data and identify relevant factors or help eliminate irrelevant ones." In order to carry out these assigned functions the public health nurse will benefit by a knowledge of hereditary disease, the basic modes of inheritance, and the social factors in the community which may influence the prevalence and distribution of hereditary disease. This knowledge can be useful in case finding, referral planning, and locating situations in the population with potential research value.

Case Finding

A knowledge of inheritance patterns of disease may be helpful in a screening program. If an individual is found to have an inherited disease, examination of other members of the kindred may reveal additional examples of this disease, thus increasing the effectiveness of the screening procedure. For example, if the mode of inheritance is recessive, at least the siblings of the initial case should be examined. If the mode of inheritance is dominant, the nurse can trace the affected individuals by history and home visits and help to establish the sibships that should be examined. These procedures can be modified for the sex-linked traits.

We have used this knowledge in an eye-screening program for chronic simple glaucoma. Studies on this disease have shown that there is an increased incidence of glaucoma among close relatives of affected individuals (Westerlund, 1947) and that it is usually inherited as an autosomal dominant trait (Sorsby, 1951). Two patients with chronic glaucoma were found during one of our routine eye surveys. The nurse then obtained a family history of eye disease, helped to establish the sibships in which glaucoma was most likely to occur, and arranged to have these people examined. Five additional cases of frank glaucoma and one glaucoma suspect were found. Two of these patients were discovered before they were aware of any eye trouble. By finding glaucoma in its incipient stages, it may be more susceptable to treatment and the damaging effects of prolonged intraocular pressure avoided.

A similar procedure has been utilized in the detection of diabetes. Because the mode of inheritance of this disease has not been definitely established, history was obtained

from the initial patients about the occurrence of diabetes, or the symptoms of diabetes, among their relatives. All siblings of any person with a suspicious history were asked to report to the clinic for urine or glucose tolerance tests. At least one additional case of this disease usually was found in the families of the initial patients.

During the early stages of a dental examination program it was noted that some of the children were tongue-tied. The teachers in the community reported that a considerable number of these children also had speech difficulties. It is not known whether the speech disorders were the result of the tongue defect, but an examination of the siblings and parents of these children showed a high prevalence of tongue-tie. These cases were referred to the speech therapist for evaluation and further study.

Referral Planning

Kemp (1956) states, "It is important for the social and public health authorities to know the number of people in their communities, who, because of hereditary disease, are incapacitated and must be given social relief, to be treated, or to be placed in hospitals or institutions." A knowledge of which diseases are genetically determined is most useful in planning public health and public assistance programs because patients with these diseases usually require long-term treatment or social aid.

In one community six families have come to our attention where both parents are heterozygous for the sickle cell gene. Thirteen children in these families have been hospitalized for varying lengths of time because of this illness. Due to the frequent need for transfusions, all of these families have been forced to call upon public facilities for medical and social aid. Several of these families have more than one member affected with sickle cell disease. Fortunately, we have been able to refer these patients to a research facility or teaching hospital in the community for care. In such instances, where several members of a family are affected with a hereditary disease requiring long-term treatment, it is advantageous to make arrangements with one facility for care of all the affected members of the family. This eliminates the need for repeated referrals. Such an arrangement is particularly desirable in cases of sickle cell disease, where the onset of a sickling crisis may be a medical emergency requiring immediate hospitalization.

In certain counties in the United States, the population is divided into more or less isolated social segments; therefore, marriages between persons with common ancestry is fairly frequent (Beale, 1957). Many of these counties have a considerable load of hereditary disease that require an expenditure of public funds. It has been reported that harelip and cleft palate are common findings in Barbour County, West Virginia (Walraven, 1957). Many of these cases were drawn from one group of families. At least twelve residents of this county, with the same surname, were treated for harelip or cleft palate during the past year. The use of public facilities and the expenditure of public funds contributed to the treatment of these patients.

The public health nurse may be the first professional person to approach a family in which hereditary disease exists. She may also be the first person to whom the family turns for information concerning hereditary illness. Because of the nature of hereditary disease and its transmission through the germ plasm, it frequently carries many emotional and psychological problems (Kallmann, 1955). A failure to understand this fact may lead to tragic results. The public health nurse, with knowledge of genetics, will recognize the need for special guidance in these situations. If an heredity counselor is available, she may refer the family to him for advice. In most communities this service is not available, so the family is referred to private physicians or hospitals for guidance in these matters.

Social Factors in the Community Influencing the Prevalence or Distribution of Intrinsic Disease

The public health nurse is in an ideal situation to observe the factors in her community which influence the prevalence or distribution of intrinsic disease. The longer she works in an area, the more familiar she becomes with a large number of family relationships, family dynamics, and the existence of particular sects or subgroups. These factors will be more apparent in a rural or suburban setting than in larger centers of population. Most hereditary disease is familial. In the community, therefore, the marriage patterns of the population will influence the distribution and occasionally the prevalence of intrinsic disease. Recessive traits usually are shown more frequently in marriages of near kin. As a result, factors that tend to limit the number of individuals among whom a person can select a mate will frequently increase the number of kin marriages in a community.

Certain generalities can be stated concerning these factors. If large metropolitan areas are disregarded, the following statements will generally hold true. Marriages between people with common ancestors will occur more frequently, the older the community; the smaller the community; the more stable the community as far as immigration and emigration are concerned; and the more geographically isolated the community (Cavalli-Sforza, 1957). Thus, in areas meeting the above criteria, recessive genetic diseases may emerge as the chances for marriages leading to homozygous offspring are increased. It does not hold true that all communities where the above conditions obtain will show this increase because there may not be deleterious recessive genes in the common ancestors. Dominant genetic traits may be prevalent in some of our older stable communities, provided they were introduced into the population by early residents of the area. Polydactylism in the newborn is occasionally seen in Charles County, Maryland; however, in adjacent Calvert County, extra digits at birth are a common occurrence.

When marriage patterns become very restrictive in any area or for a given group of people, and these restricted patterns are continued over a period of several generations, an isolate results (Sutter, *et al.*, 1957). In an isolate there is a chance that any two individuals who marry are related through some common ancestor, and, therefore, the possibility exists that they share common genetic material. Isolates are not uncommon in this country. As examples, there are numerous small religious groups that permit marriages only within that religion. These groups remain relatively small and retain approximately the same genetic composition, as only a few new converts are admitted each generation. Thus, after a time, nearly everyone is related to everyone else. The Hutterites of the western United States and Canada and the Dunkers of Pennsylvania are examples of such groups. In the latter some striking genetic differences from the general population of approximately the same racial stock have been noted (Glass, 1953).

Certain racial groups have formed primarily in the eastern part of the United States and are termed racial isolates. Some twenty-six of these groups have been identified (Witkop, 1956, 1957). Their marriage patterns are limited as they are outside the usual racial classifications of White, Negro, Indian, or Oriental. As a result these people have married within only a few families for generations and show a very high prevalence of intrinsic disease (Hursey, *et al.*, 1956).

Public Health Nurses in a Research Program

The Human Genetics Section of the National Institute of Dental Research has been conducting an investigation into the dental, medical, genetic and social aspects of a population isolate residing in Mary-

land (Witkop, *et al.*, 1956). This group consists of about 5,000 individuals of Caucasian, Negro and American Indian ancestry, who have been regarded as a separate racial class since before 1760. These people were not accepted into the white community and did not consider themselves Negroes. As a result, they marry, for the most part, within fourteen surnames, of which only seven are common. The purpose of this study is to find all of the hereditary disease present in this population.

This study is divided into three phases. In phase one, public health nurses obtain genetic, social, and medical histories from each individual by interviewing all persons over sixteen years of age. They arrange these data by family groups and by sibships. In phase two, each individual receives a medical, dental and eye examination in the field. Blood, urine and saliva specimens are obtained for various tests. In phase three, selected individuals are brought into the Clinical Center for detailed studies. Analyses of these data are to be made by I.B.M. tabulation.

Public health nurses were selected to participate in this investigation because their professional training and field experience could be utilized in all phases of the study. They had sufficient knowledge of the signs and symptoms of disease to obtain an adequate preliminary medical and dental history. They could utilize their clinical training during the field examinations and hospital studies. One nurse had worked with these people previously, had established a good rapport with the families, and provided the necessary *entree* into the group.

The nurses selected to participate in this program were given a four-week training course at the University of Michigan and the National Institutes of Health. This program included introductory genetics, medical genetics, elementary statistics and interviewing techniques. This program was followed with a two-month period in the field under the supervision of an experienced investigator. The study required that the nurses obtain a kindred chart, a household census, and a medical and social history of each family. The medical history was taken in the form of a questionnarie covering 158 items. Because all the hereditary diseases of the people were not known at the beginning of the study, it was necessary that both the medical and social interview be as open as possible to allow additional information to be obtained from the informant and recorded on the questionnaire. The results of each pregnancy were recorded.

Interviewing

It soon became apparent that there were considerable variations in the economic and educational levels, even among siblings, in this group. The nurse endeavored to obtain the initial kindred and census data from the most responsible and best-informed person in the family group. This method of approach was of considerable importance as the attitude of the initial contact often determined the degree of cooperation she received from the rest of the family. The objectives of the study and the method of recording the information in code to protect the identity of the family was explained. Each member of the family over sixteen years of age was interviewed separately, if possible. The information received from one individual was checked against that obtained from the siblings and parents. In this manner we frequently were able to obtain fairly reliable information on stillbirths, miscarriages and illegitimacy.

The social information was then verified from birth and marriage records obtained by the sociologist. The verified data was given to the geneticist who is constructing a kindred chart of the entire group. One of our most difficult problems is to identify individuals, many with the same given name, in a group with only fourteen surnames. The magnitude of this problem can be imagined when it is realized that in a

104-year period, in one parish, 129 family "A" men married a group member in all but ten instances. Of these marriages, 40 per cent were to family "A" women and 20 per cent to family "B" women. Thus 92 per cent of the marriages were endogamous. In this same 104-year period, 17 per cent of the group marriages required ecclesiastical dispensation for relationship (Harte, 1957). The large size of the families also makes it difficult to trace all lines of relationship. A direct estimate of family size from our sibship schedules indicates that the average woman had about 5.7 offspring between the years 1900 and 1950. These sibships ranged in size from none to twenty-two individuals.

Field Examinations

During the summer months field examinations were conducted. Two trailers were equipped for medical examinations and one for dental examinations. It was the responsibility of the nurses to equip and maintain all examination facilities. Six recorders were trained and supervised by the nurses. It was the duty of the nurses to make appointments for entire family groups, collect blood, urine and saliva samples, and administer phenylthiocarbamide taste tests.

The results of these investigations show a large amount of hereditary disease among these people. The three most common intrinsic diseases found to date are *dentinogenesis imperfecta* — 171 cases, sickle-cell trait or disease—118 cases, and albinism—55 cases. Twenty-two other inherited conditions, or conditions in which genetic factors are suspected, occur in this group.

Heredity Counseling Problems

We would like to raise several questions for discussion at this symposium concerning heredity counseling in isolate populations. Since the initiation of this study the subjects of this investigation have become aware that their hereditary diseases are somewhat unusual. Many questions are put to us by these people, the local physicians and the public health authorities.

In one family the parents are at least third cousins. The mother has an external ear defect and *dentinogenesis imperfecta*. She has had three children and is expecting a fourth. All three children have *dentinogenesis imperfecta*. Two have defects of the external ear which is transmitted as a dominant trait. Two are also deaf-mutes and require special schooling. Two of the father's maternal uncles are also deaf mutes. The county health officials ask us if the mother should have more children.

A 38-year-old woman in her eighteenth pregnancy asks our opinion about sterilization. Two of her children are albinos. The family is barely able to subsist on an income of $42.00 a week. The family physician recommends sterilization, but this conflicts with her religious teachings.

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The questions we would like to raise are: Does the heredity counselor present the facts about the risks involved and let the individuals decide upon a course of action, or does he recommend that certain measures be taken? What advice is to be given to young people contemplating marriage within an isolate group? The answers to these questions involve counseling of an entire population rather than individuals when the facts of social and religious restrictions make it difficult to find an acceptable marriage partner outside the group. At least 77,000 people in this county are members of such racial isolates and are faced with this problem.

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DISCUSSION

Chairman Bugher: This is a fascinating presentation of the most intriguing information. One can't help but reflect on the factor in this whole problem which has not previously been mentioned—that of the social values in a given society of what we call anomalies or defects which sometimes may not necessarily be disadvantageous to the individual, depending on the attitudes and the value schemes of his own society. I was thinking of an instance in my own acquaintance. In West Central Africa having twins is almost the ultimate family disaster, so you do not find twins. Invariably either one or both will be killed immediately. On the other hand, among the tribes in Uganda, on the eastern side of the Continent, no greater distinction can befall the father of a family than to be the father of twins. If a man fathers twins, he may take the name of Asumani and may carry that name throughout his life as a great badge of distinction.

This paper is open for discussion and questions. I'm sure there are bound to be many questions which are suggested by this very interesting collection of data.

DR. JOHN D. RAINER: At the Psychiatric Institute under Dr. Kallmann we are making a similar survey of a different kind of isolate, made up of deaf people in New York State: people who have been born deaf, or people who have become deaf in very early childhood.

Of course this group tends to intermarry and tends to make a value out of a defect, and here we find some of the same problems that Mrs. Dyson found. I wonder specifically if she could tell whether there was a specific relationship between albinism and deafness in the group in Maryland.

MRS. DYSON: No, there is none.

MR. FREDERICK OSBORN: I wonder if Mrs. Dyson got any impression as to whether the people in this group would accept advice and would be amenable to voluntary steps to act on your advice.

MRS. DYSON: Yes, I think so, in some cases, but actually we don't feel that we're qualified to give them definite advice. But we do believe they have confidence in us because they usually come to us first. We then like to follow through and go back to see them so we can establish good relations with them for further work.

CHAIRMAN BUGHER: I had the impression from the material of this presentation that these isolate societies, for the most part, tend to be in areas where the general level of medical care may be below that of most of the country, and certainly below that enjoyed by many urban populations.

Heredity counseling would seem to require a rather sophisticated medical and nursing profession, and I think it's not unfair to say that most of the practicing medical profession at the present time—those who graduated a certain number of years ago—do not have the technical background in genetics to appreciate all these problems. Perhaps the people who need counseling to the greatest extent are the ones who have the least access to such counsel. Is that the case, or not?

DR. WITKOP: One large group lives right next to Bowman Gray Medical School. Quite a few of these people that we're dealing with are not too far from Johns Hopkins. Part of the isolate we are investigating resides in the District of Columbia, but, for the most part, these isolates are fairly remote from any counseling facilities. Some groups are fairly close to Ohio State, and some near the University of Pennsylvania. In the southern part of the country the people frequently do not have adequate medical care, especially the Negro population. These people are often classified or lumped together with the Negro population. That is not invariably true, because some of them go as white in the census figure. However, for the most part, many of them in the Appalachian Chain are in remote areas. In no place do these populations constitute more than 10 per cent in one county except in certain areas in the Carolinas where they may be as high as 70 per cent.

DR. ALAN F. GUTTMACHER: Of course, if you are going to give advice and it's negative advice, that means sterilization or contraception. Are there facilities in these areas where such advice can be carried out?

DR. WITKOP: In some of these areas some of the people are not of an economic or cultural level to accept that advice. Also in some of the groups it will conflict with their religious teachings. So, rather than give them any positive advice, we have been referring them back to their physicians with whatever burdening questions they have. The trouble is that the physicians turn around and call us for genetic information.

CHAIRMAN BUGHER: We will continue with our next paper, which goes back into an area where morphology is present as a genetic manifestation, but we also have the intermingling of a great deal of the functional. Dr. Victor McKusick is here to present his paper on "Genetics in Relation to Cardiovascular Diseases."

GENETICS IN RELATION TO CARDIOVASCULAR DISEASES

VICTOR A. MCKUSICK, M.D.
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IN 1745 Lancisi remarked on the occurrence of aneurism of the heart, his term for cardiomegaly, in male members of three generations. Over a century earlier Peter Forestus had described a familial incidence of cerebral hemorrhage. In his *magnum* opus, Morgaeni described the cerebral hemorrhage of one Zani whose father had likewise died of "apoplexy." In moments of gloom, I think we are very little removed from the position of these writers of two and three centuries ago: Heart diseases tend to "run in families." My charge in this symposium, as I interpret it, is to survey in birds-eye manner how much further ahead, if at all, we are.

Probably all would agree that some genetic influence is involved in the pathogenesis of all four of the major varieties of cardiovascular disease: congenital malformations of the cardiovascular system, rheumatic fever, hypertension, and atherosclerosis, including coronary artery disease. Clearer operation of genetic factors is seen in the rare varieties of heart involvement occurring as part of tuberous sclerosis, the syndromes of Marfan and of Hurler, glycogen disease of the heart, progressive muscular dystrophy, myotonic dystrophy and Friedreich's ataxia. But we will confine our remarks to the Big Four.

For many reasons, the genetic factor is extraordinarily difficult to study in these disorders. Probably in no other major category of disease is multifactorial causation so complex. The multiple factors are both environmental and genetic. Obviously to state that genetic factors of some significance are involved in rheumatic fever does not deny the role of the streptococcus. To say that heredity is significant in atherosclerosis does not deny the significance of diet. To point out a genetic factor in congenital heart disease does not exclude the important role of the intra-uterine environment, *e.g.*, with reference to maternal infection.

The two biggest of the Big Four, hypertension and atherosclerosis, are not independent operators. Each potentiates the other and study of one must take the other into consideration.

In the case of rheumatic fever, heredity presumably determines why only certain of those individuals exposed to the appropriate streptococcus develop the disease. Were there a method for identifying the genetically susceptible individual, it might be possible to provide more economic and effective prophylaxis, especially to individuals in high-risk environmental situations such as barrack life. It would be of great interest, both theoretical and practical, to know what distinguishes the "rheumatophilic" individual from the general population and to know the mechanism of the genetic enhancement of susceptibility to rheumatic fever.

Although there are data which appear to leave no doubt of a genetic factor in this disease, rheumatic fever illustrates how easy it is to misinterpret certain observations as indicating a genetic basis. The idea emanated from Boston a few decades ago that persons with red hair, fair skin, freckles and blue eyes are more susceptible to rheumatic fever, presumably because of genetic constitution. This conclusion was probably based on the character of the Boston population at that time. Beginning in the middle of the last century, large numbers of Irish families immigrated. They lived under crowded and undernourished circumstances ideal for the development of rheu-

matic fever. Later as Irish immigration waned and the Irish already in Boston became more prosperous, immigration from southern Italy and Sicily increased. Families of Italian origin took over the cold-water flats, crowded living facilities and pick-and-shovel work. *Pari passu* the complexion of rheumatic fever in Boston changed, quite literally.

In recent years several excellent studies on the genetics of congenital malformations of the heart and great vessels have established the following generalizations:

1. An aggregation of cases in sibships occurs such that the incidence of cases among the sibs of probands is on the average increased 10 to 15 times over that in the general population and in the case of some types of malformation, 40 times.

2. The consanguinity rate is increased in the parents.

3. Congenital malformations of the heart occur rarely in two successive generations.

4. There is some increased concordance in monozygotic twins as compared with dizygotic.

5. There is an increased incidence among the first cousins of the probands.

6. About one-fifth of the cases, regardless of the specific type of the cardiovascular malformation, show other congenital malformations.

There is not complete agreement as to how much intrafamilial similarity there is in the variety of malformation.

Two general observations may be made. It is essential to consider the precise type of malformation separately. The genetic factor appears to be less important in some malformations, such as simple ventricular septal defect, than in others, such as pure pulmonary stenosis or patent ductus arteriosus. Intrafamilial similarities are more striking for some. Some malformations, specifically coarctation and patent ductus arteriosus, are at times transmitted through successive generations. As a result of the large concentrations of congenital heart cases in places such as Paris (1), London (2) and Baltimore (3), excellent empiric risk figures are becoming available.

TABLE I

CROSS-BEAK IN CHICKENS

Breed	*Sporadic Incidence*	*After 40 mgm/egg ethyl carbamate*
White Leghorn	0.20%	6.8%
Black Minorca	1.63%	25.4%

HARELIP AND CLEFT PALATE IN MICE

Strain	*Sporadic Incidence*	*After Cortisone to Mother*
1	5.0%	100%
2	0.2%	18.7%

(After Landauer)

A second point: one is reminded of the work of Landauer and others (Table I), who can produce congenital malformations with teratogenic agents with varying facility depending on the genetic strain of the experimental animal. Ethyl carbamate produces cross-beak in 6.8 per cent of white leghorns and 25.4 per cent of black Minorca. Comparing two strains of mice, one with a 5 per cent sporadic incidence of cleft palate and harelip and another with a 0.2 per cent incidence, it is found (4) that cortisone produces a 100 per cent incidence in the 5 per cent sporadic group and only 18.7 per cent in the other. Genetic and intrauterine environmental factors may well collaborate in the production of congenital malformations of the cardiovascular system, as in other congenital malformations (11) —one is reminded immediately of Mongolism.

The chart in Figure I is intended to indicate some of the factors responsible for atherosclerosis. I do not apologize one whit for its complexity, since this is the nature of the problem and this chart is doubtless already a gross over-simplification. Both the environmental and genetic factors are multiple. The proportions of each varies from case to case. Stress may contribute to hypertension and possibly even to hypercholesterolemia, both of which ac-

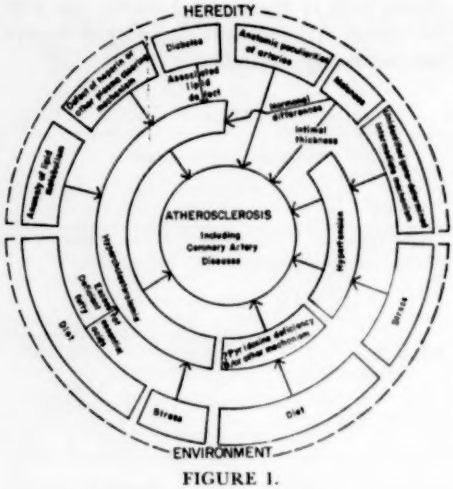

FIGURE 1.

celerate atherosclerosis. Diet, by reason of excess fats or the wrong kind of fat, perhaps by reason of deficiencies of pyridoxine, and possibly by other mechanisms not now known, may contribute to atherosclerosis. The genetic predisposition to atherosclerosis may operate through many avenues. Diabetes with its associated defect of lipid metabolism is one mechanism or perhaps a cluster of genetic mechanisms. Parenthetically, diabetes, *per se* exceedingly difficult of genetic analysis, illustrates how much more complex is the problem of atherosclerosis, to which it is but one contributing factor.

Probably variations in the pattern of distribution of arteries, such as the coronary and the cerebral, are to some extent genetically determined. These variations may be critical in determining the clinical effects of thrombosis and possibly some varieties may predipose to atherosclerosis through hemodynamic peculiarities. Accumulation of data on intrafamilial similarities of coronary or cerebral arterial patterns is difficult, requiring, as it does at present, necropsy determination. Wilkinson (13) postulates that atherosclerosis is "a process in which an inherited defect of arterial structure permits the development of placques under the influence of secondary factors, such as hypertension, renal disease, and certain hormone imbalances." He pictures this arterial abnormality as "an inherent defect at the junction of the intima and media." This suggestion should stimulate productive work. It *is* known that the coronary arteries of the male have a greater intimal thickness than those of the female from the early stages of development. Some families have a genetic defect of lipid metabolism, leading to hypercholesterolemia, in such pronounced form that it is possible to analyze this factor which overshadows the others. Reference is made to the work of Adlersberg (5), Wilkinson (6), and others (7). A genetic defect in the plasma-clearing mechanism is only speculative. There are other factors which influence blood lipids but are not covered in Figure 1, e.g., exercise and hormones.

The family history is of utmost importance in *diagnosing* coronary artery disease, let us say in a young man with chest pain, and in the *planning* of a dietary or other program for an individual or a family. In a recent joint report (8) the statement was made: "The evidence at present does not convey any specific implications for drastic dietary changes, specifically in the quantity or type of fat in the diet of the general population, on the premise that such changes will definitely lessen the incidence of coronary or cerebral disease." However, the report does state: "These conclusions obviously apply to the general population, and not to patients or to individuals with a strong family history of early deaths from cardiovascular disease." One is reminded of the well-known story of the man accused of stealing a jug: "Why, I have never as much as seen that jug; furthermore, it was cracked anyway."

The young coronary artery patient has been the object of study by several groups, including Yater (12) who used an army population, and by Gertler, White and others (9) who used a hospital and private practice population. Such studies demonstrate peculiarities which may have a gene-

tic basis. For example, Gertler and colleagues (9) found a deficiency of ectomorphic individuals in the young coronary population.

For prognosis and prevention, we should have information on what the young coronary victim looks like as a child and teenager. For this reason, we have undertaken to focus on the children of young coronary patients as much as on the proband.

In essential hypertension we again encounter the problem of multifactorial causation which is probably in part environmental, in part genetic. There is some reason to think that blood pressure is a continuous variable, which is age and sex dependent. The state we choose to designate hypertension is the arbitrary truncation of a distribution curve.

As in the case of atherosclerosis, in which the genetic factor is easiest to demonstrate in young coronary artery patients and in patients with a striking lipid defect overshadowing all other factors, so in hypertension the neatest category for study would appear to be malignant hypertension, that is, accelerated phase of essential hypertension. Some workers find a striking family history of hypertension in the majority of cases of malignant hypertension; when such a history is absent, primary renal disease or similar specific cause of the hypertension is suspected. (The results of some other workers are not in agreement, however.)

Pharmacology has two major divisions. One concerns itself with the question of whether a given drug is effective, the other with the mechanism of drug action. In clinical genetics we have a comparable dichotomy: Is there a genetic factor in a given disorder? What is the mechanism by which a genetic factor operates in the production of a given pathophenotype?

In our department Humphreys has recently demonstrated, by an ingenious method, the heritability of a tendency to hypertensive toxemia of pregnancy. He studied 100 toxemic women who were themselves born in the Johns Hopkins Hospital, and whose mothers, by reason of the latter fact, were observed at that hospital during at least one pregnancy. When he compared this group with a similar group of 100 non-toxemic women, likewise born in the Johns Hopkins Hospital, Humphreys found an incidence of hypertensive toxemic over 2½ times greater in the mothers of toxemic daughters than in the mothers of normotensive daughters (Table 2).

TABLE 2

	Number in Group	*Experienced Toxemia*	*Born of Toxemic Pregnancies*
Probands	100	100	28
Controls	100	0	11

Thus, a familial and very likely a genetic factor has been demonstrated, but what is its mechanism, how do the toxemic lines differ from the non-toxemic lines?

Another colleague of mine, Caroline Bedell Thomas (10) has proposed certain guideposts in the prevention of heart disease of the hypertensive and atherosclerotic types. These guideposts are derived from the experience of others and from her own in the study of Johns Hopkins medical students. Dr. Thomas grades the probability of developing cardiovascular disease in four classes, depending on the parental history for hypertension and coronary artery disease and on certain traits displayed by the individuals. These traits probably also have, in considerable degree, a genetic basis. Inexact and empiric as it is, this type of approach is one of the best we have for guiding preventive measures at the clinical level, that is, at the level of the individual. In effect, it is an attempt to place on a more concrete basis that vague quantity known as "clinical judgment." A genetic assessment enables the susceptible individual to be pin-pointed and prophylactic measures to be arrived more effectively.

There is a prevalent conception that demonstration of a genetic factor means that treatment is hopeless. It is not necessary to point out to this group that such

pessimism is unwarranted, that the ability to identify genetic susceptibles is the most promising attack on many of the major illnesses with which mankind is presently afflicted, and that solutions to these problems through preventive medicine will be closer when characterization of the genetic factor is complete.

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DISCUSSION

CHAIRMAN BUGHER: We have a very few minutes here for additional discussion and questions.

DR. MCKUSICK: I am prompted to ask Dr. Warkany whether he investigated the family history of cleft palate due to aminopterin, or whether the family history in any of these aminopterin-induced abortions has been looked into.

DR. WARKANY: I did not ask about cleft palate in this family as yet. At the time this child was born the conditions were not favorable for obtaining a good family history. However, I would like to say one word about the concept that teratogenic factors just increase the incidence of malformations that occur in certain stocks spontaneously and sporadically. You showed Dr. Fraser's figures where this seems to be borne out, since in the strain of inbred mice where cleft palate occurs spontaneously a higher incidence was produced by cortisone than in the strain that does not show these anomalies without treatment. This to my knowledge has not general significance. We have Dr. Fraser and Dr. Kalter here, who can discuss that much better, and I wonder if they could say something about that point.

DR. H. KALTER: First, it should be remembered that the spontaneous anomaly occurring in the A strain of mice is cleft lip with or without cleft palate, whereas the cortisone-induced malformation is cleft palate without cleft lip, and that the embryogenesis of these conditions is different from each other. Second, although the A strain is more susceptible to cortisone-induced cleft palate than are the DBA and C57BL/6 strains, which do not have spontaneous cleft lip, A mice are not always more susceptible than the latter strains to the cleft palate-inducing properties of teratogens, as has been shown by our recent experiments using riboflavin deficiency.

A clear though not always recognized mor-

phological and embryological distinction exists between cleft lip versus cleft palate, which may not always exist between other spontaneous and induced anomalies that closely resemble each other. But until the detailed pathogenesis and morphology of the similar conditions is worked out, it is not legitimate to assume that the teratogen has merely increased th eincidence of the spontaneous malformation.

CHAIRMAN BUGHER: I don't think that anyone could very successfully dispute the value of as many accurate observations as possible in the family history with respect to any of these matters.

DR. ALLEN: I don't think this matter should be left very definitely one way or the other. There is a wealth of information from experimental genetics about production of defects as phenocopies in just those strains that are genetically disposed to the same defects spontaneously. There are therefore grounds for assuming a predisposition, as well as for questioning it, in any particular instance of defect.

COMMENT: In Dr. Warkany and Dr. Kalter and Dr. McKusick, I see a tendency toward an all-or-none type thinking, which is not good for consultant purposes. Very often, it seems to me, heredity is assigned causation by default.

If the investigator or the counselor has failed to recognize that they have a case where they can't identify anything genetic, that is, a family history, do you have any assurance at all, if you can identify neither family history nor etiologic environmental agents, in saying that it isn't going to happen again? In other words, you are as much in the dark with the environmental agents as you are with the so-called genetic factors.

As to the aminopterin-induced abnormality: if you can identify something environmental that is unusual, are we any more certain that we may ascribe with justification anything that may happen to the environmental than to the genetic?

DR. GLASS: I dislike to refer to my own work, but since the challenge has been thrown out I would like to point out that there are cases in genetics which have been studied for many years and which show very clearly indeed that the ability for the production of various kinds of abnormal growth is dependent upon the presence of a particular genetic basis. Let me refer the commentator to a paper published just two weeks ago in *Science*.

DR. C. NASH HERNDON: I would like to ask if these two concepts are in any way mutually incompatible.

DR. GLASS: Not at all.

DR. HERNDON: It seems to me that, if one considers the question of penetrance of genes, it is not unlikely that environmental stress of a wide variety of types could bring a gene normally not penetrant into a penetrable state, and, similarly, that one might induce a clinically indistinguishable effect by a teratogenic agent.

DR. POTTER: I'd like to change the subject just a little bit and comment on one of the tables Dr. McKusick showed in relation to the babies who were born of toxemic pregnancies. I would like to know whether they have separated the two types of toxemia. I think it's generally accepted that you have one form, preeclamptic toxemia, which differs from hypertensive toxemia, and if you lump the two together you probably get into a state where you have relatively little information.

Is this hypertensive toxemia? And if it is, is it primarily a manifestation of the importance of a hypertensive background rather than toxemia proper? Is it preeclamptic toxemia, or is it a combination of both?

DR. MCKUSICK: I would like very much to go over all these data with you, but in general the hypertensive toxemia for the purposes of this study was defined in terms of blood pressure only, and diastolic blood pressure in excess of 90 was the criterion. Systolic blood pressure was not used because of apparent variability on exogenous bases. No one was included in the study who, by any evidence, was a chronic hypertensive on any other basis, such as pyelonephritis.

Another aspect of the study was a follow-up on the mothers of these women, done exclusive-

ly, with the obvious difficulties, through the unit records of the patients which, of course, meant that every visit to the hospital was incorporated in the same record. So 60 or 65 per cent in each group had ten-year follow-ups, and something approximating half that figure had 20-year follow-ups. There is a statistically significant greater incidence of hypertension in the mothers of toxemic daughters. There also is, however, this same situation in the toxemic mothers of normal daughters, and I think this fits together. We interpreted this finding as indicating that hypertensive toxemia of pregnancy is one expression of a familial tendency to hypertension of the more conventional, or perhaps the regular, variety.

CHAIRMAN BUGHER: I think that this brings us to the end of our allotted time for the morning session. I'm sure that I speak for everyone here in thanking our speakers for their generosity and helpfulness and labor in laying before us all of this extremely interesting and valuable material and comment.

Now, I hope that perhaps Mr. Osborn may have a suggestion as to the next order of events here.

MR. OSBORN: The next order of business is lunch. We want everybody to know that there's a buffet luncheon downstairs, to which everyone is invited and to which we all may help ourselves.

HEREDITY COUNSELING PANEL

(Ten-minute presentations with discussion)

Afternoon Session

Chairman: *Bentley Glass*

CHAIRMAN GLASS: I think the setting for the panel's consideration this afternoon has been laid very well by the program of the morning. I would like to say one thing before I ask the first person on the panel to present his opinion on the subject announced.

At Stanford this summer in an address that I was asked to give on the responsibilities of biologists, I made a rash statement to the effect that the biological discoveries of the next decade or so were likely to be as revolutionary in their impact on society as the developments of the atomic physicists during the past few decades. But I didn't go into any analysis or discussion or description or prophetic intonation to spell out what these revolutionary discoveries in biology that are just around the corner might be. The newspaper reporters, hopping on this and thinking that this would surely be news, were very much distressed that I wouldn't take on the role of a prophet.

Here, in a smaller company, where I hope no newspaper reporters are listening in, I might be somewhat more rash, because I think it's relevant to this topic of heredity counseling. I think we can't look just at the situation as it exists at the present time and at the problems that confront those who want to give advice in respect to heredity to inquirers. We have also necessarily got to look 10 or 20 years ahead, if we can with reason do that, and begin thinking about the problems that are going to face heredity counseling then, and what responsibilities will rest upon those who take on this role.

I might suggest, for instance, that the impact of effective control over conception—the development of new steroid pills which can produce complete, temporary abeyance of menstruation —is one thing that is going to alter the picture very considerably in this and related fields of population problems. Not only is this harmless and effective contraceptive going to bring about a very radical change, but the techniques of artificial insemination which have been so well developed by the cattle breeders offer possibilities again with respect to the human population that raise legal and ethical problems that the heredity counselor is also certain to become concerned with.

I often think that it is a good thing, perhaps, that Lysenko was in power in Soviet Russia during the days of Stalin, who had a certain desire to see his own offspring live after him. The possibilities of freezing semen and using artificial insemination after considerable periods of time raise possibilities that perhaps the science fiction writer has dealt with but that we might actually have had to face up to.

And then, if there is any credence to be placed at all in the reports of artificial parthenogenesis in mammals—(I'm not referring to the discussion that took place in the newspapers in Great Britain last year but rather to the experiments of Pincus and Chang with rabbits)—if parthenogenetic rabbits have been produced —then it would seem theoretically that there can be no reason why parthenogenesis couldn't be employed in the human species, too. This also raises questions that may lie ahead of us in the future.

This month in the proceedings of the National Academy of Sciences there is a paper on the separation by electrophoresis into male-determining and female-determining elements in the spermatozoa of the rabbit, not with com-

plete efficiency but with sufficient efficiency so that if the method can be applied to human semen it seems possible that artificial control of sex determination is not too far around the corner. What kind of advice are we going to give when we are faced with problems in this area?

And last summer there was an even more startling announcement from biologists in France, who reported that, by inoculating into the eggs of young ducklings of one genetic strains of ducks an extract of desoxyribose nucleic acid from a different strain they were able to bring about a transformation of the genetic type. This has not been confirmed yet. Whether actual transformation of genes or of the effects of genes can be brought about in this way is not clear, but with recent developments and methods of artificially synthesizing the hereditary material of bacteria it seems certain that within a few years we will have a much better knowledge than we do now of the chemical structure of the hereditary material. And if a transduction is a phenomenon that you can find in higher animals as well as in bacteria, it seems possible that we might eventually be substituting desirable for undesirable genes in the germ cells of certain genotypes.

These are problems that I'm sure the members of the panel are not likely to want to discuss this afternoon. I just suggest that heredity counseling is, in the next few decades, going to steer into stormy waters. If we can give some thinking to these problems in advance and clear up questions of our own ethics in relation to such things, we may be better prepared when the time comes.

The questions which have been posed to our panel this afternoon relate to the problems of heredity counseling as the problem now exists, and I feel sure that within this area we will still have quite enough to dispute about this afternoon. We should all have a sufficiently lively time.

The first speaker is Professor Lee R. Dice, who, more than any other, I think, was instrumental in the establishment of the work in human genetics that has developed to such a splendid extent at the University of Michigan. Professor Dice is going to discuss the structure of heredity counseling services.

THE STRUCTURE OF HEREDITY COUNSELING SERVICES

Lee R. Dice
Department of Zoology
University of Michigan

When it is desired to organize an heredity counseling service the first question asked is: "What facilities are needed to organize such a service?" This is not an easy question to answer because local situations vary greatly. As a partial answer I submit the conclusions I have reached from my own experience in organizing an heredity clinic at the University of Michigan.

Personnel is the most important factor in any effective counseling service, so let us first consider the staff. At least one staff member of the service must, of course, be thoroughly versed in human genetics. This geneticist must be competent to analyze family pedigrees and to ascertain, so far as may be possible, the mode of heredity of the trait or traits in question in each particular kindred under consideration.

Many of the questions asked of a counseling service pertain to medical traits. Diagnoses of the affected members of each kindred must be obtained or verified. The presumed normal members must usually be examined also in order to be certain that no affected individual is mistakenly classed as unaffected. These diagnoses and examinations require the services of one or more physicians, who often must be assisted by clinical laboratories of various kinds.

The minimum professional staff of an heredity counseling service is, consequently, one human geneticist and one physician. Neither of these persons need necessarily work full time in providing counseling service, but they must be able to work together as a functioning team. The most favorable situation is where the heredity counselor is at the same time both a human geneticist and a doctor of medicine. Unfortunately, very few persons have this combined training. Usually, therefore, the geneticist must be a different person from the physician.

Not every geneticist with special training in human heredity nor every physician will make a successful genetic counselor. A broad sympathy with human frailties is needed as well as knowledge of the wide distribution of human defects. The counselor must be able to give due weight to all the hereditary features of each kindred which comes to him for advice. He must be able tactfully to call attention to the average and to the superior heredity which the family carries as well as the particular defect which has brought the family to his attention.

In addition to the professional staff of geneticist and physician, an heredity clinic needs a secretary to copy and file records, answer correspondence, make appointments, and otherwise keep the work running smoothly. A laboratory assistant to draw pedigrees, make photographs, type bloods, and do other related types of laboratory work can be of great help. For certain kinds of study there may also be needed a field worker who can visit relatives in their homes and make appointments for certain of them to come to the clinic for examination or for the physician to examine them in their homes, if this is possible.

An heredity counseling service need not always be organized as a special administrative unit. Counsel in heredity is being given by a number of human geneticists who are not associated with any organized counseling service. Cooperation with one or more physicians is nearly always required. A disadavantage of such an arrangement is that, lacking a formal organization, the service will probably be discontinued when either the geneticist or the cooperating physician is unable to continue. A handicap is that the geneticist may find difficulty in securing access to all the confidential medical information he may need to complete his pedigree analyses. Furthermore, such cooperative undertakings must usually be on a part-time basis for the staff members and one or more of them may find difficulty giving the work the attention it needs. For these reasons, I strongly recommend that every heredity counseling service be organized on a permanent basis with adequate staff to provide the needed service.

The most favorable location for an heredity counseling service is in association with a well-equipped hospital. The Heredity Clinic of the University of Michigan operates as a unit of the University Hospital and has the same position as any other of the hospital clinics. This favorable administrative location gives the staff of the clinic access to the hospital records, use of the clinical facilities of the hospital laboratories, and freedom to ask advice from any of the members of the hospital professional staff. Conversely, the hospital staff may easily refer their patients to the Heredity Clinic for advice about heredity.

Financial support for any heredity counseling service is difficult to secure. Few persons would be willing or able to pay the considerable expense required to make the necessary examinations and diagnoses of their relatives before dependable advice about their heredity could be given. Those families most in need of genetic advice often are the very ones least able to pay for it. Furthermore, many of those individuals who greatly need counsel about their heredity are so little interested in the subject that they would refuse to pay any fee at all.

The Heredity Clinic of the University

of Michigan is supported through the Medical School as a part of the training of medical students and to provide material for research in human genetics. Heredity counseling services elsewhere are supported in various other ways.

This problem of financial support for heredity counseling needs much careful consideration and experiment. Probably the problem will be solved differently by different communities.

Human heredity actually is a phase of public health. The heredity of the population should be of at least as much concern to each commonwealth as are infectious diseases. I look forward to the time when heredity counseling will be available in every large center of population. Such a development, however, is not likely to be achieved in the near future. For one thing, it would be impossible to staff more than a few such services with the geneticists now available who have had training in genetic counseling.

Interest in genetic counseling, however is rapidly spreading. Knowledge of the mode of heredity of human defects also is expanding. It is only a question of time, in my opinion, before heredity counseling service will be demanded by communities all over the nation.

DISCUSSION

CHAIRMAN GLASS: To keep our discussion focused on the entire presentation of the panel, I think it will be better for us to reserve the main discussion until after the presentation of topics. But we can take time, as each speaker concludes, to ask any questions for specific clarification.

The second speaker on the panel is the man directly responsible for the development of the Department of Human Genetics at the University of Michigan, Dr. James V. Neel.

My own most intimate period of acquaintance with Jim Neel was when he was struggling with something that had gotten into his *Drosophila* stock that was making genes mutate at a fantastic rate. Whether it was a gene that was doing this, or, as we might now suspect, some kind of a virus that had gotten in there and become attached to the chromosome, no one can say. But, from very interesting work on *Drosophila,* Dr. Neel decided that he wanted to go into the field of human genetics. He had the courage to relinquish an established program in the genetics of *Drosophila* and enter medical school as a student to prepare himself for an ambivalent kind of career in human genetics.

I think it's rather interesting that among those who are on this panel I believe the majority started out as workers on some more lowly organism than *Homo sapiens.* And perhaps that is a good thing—not necessarily an essential thing—but I hope, personally, that always we will have in the field of human genetics a sufficient number of individuals who have had an experimental basis for their understanding of the intricacies of human genetics.

This is an interesting topic that Dr. Neel has been asked to discuss this afternoon. It's already been raised this morning: "The Meaning of Empiric Risk Figures for Disease or Defect." I know that other members of the panel have been working on this same problem and are anxious to hear what Dr. Neel is going to say.

DR. JAMES V. NEEL: For the benefit of you who do not know the background, I cannot resist taking this opportunity to point out the rare authority which the previous speaker brought to his presentation. Dr. Dice was responsible for getting the first human heredity clinic in this country under way in 1941. Scarcely a month passes now but that we who are carrying on with the Clinic he founded get an inquiry from some place as to how you organize such an undertaking. These inquiries, as well as this very symposium, must, I'm sure, be a tremendous source of satisfaction to Dr. Dice as he looks back 16 or 17 years.

All I have been asked to do this afternoon is to define empiric risk figures. Other speakers will deal with the problem of how we use these figures. My function is all the easier, because Dr. Warkany, in effect, gave my talk for me this morning, but I will go over again some of the things that he said earlier.

THE MEANING OF EMPIRIC RISK FIGURES FOR DISEASE OR DEFECT

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IN GENETIC COUNSELING extensive recourse is had to "empiric risk figures." In general, such figures are statements, based on experience rather than an understanding of etiological mechanisms, of the likelihood that a particular condition will be present or develop in a particular individual under a particular set of circumstances. For example, we have empiric risk figures for the likelihood of the recurrence of a child with a harelip, once such a child has been born to parents normal in this respect, whose antecedents were likewise without the trait. Or, using the same trait as an example, we have empiric risk figures for the likelihood that when an individual with a harelip marries a normal individual, the children of this union may be expected to exhibit this trait.

Empiric risk figures are usually assembled as follows: an investigator interested in a particular trait, say harelip, takes a careful family history each time he examines an affected individual. Let us say that he finds that 100 such individuals, all born of normal parents, have 300 siblings, of whom 15 exhibit a harelip. The empiric risk of encountering this trait among the siblings of an affected individual is thus 5 per cent, and this risk could then be applied to the probability of any future siblings of such an individual exhibiting the defect.

A question which often arises in the derivation of risk figures is whether all the siblings of an affected individual should enter into the derivation of the risk figures, or only those born subsequent to the affected propositus. Many of the empiric risk figures in the medical literature have made use of all siblings. In so doing, there is the tacit assumption that the risk remains constant with parental age and parity. With respect to congenital malformations, a class of defects for which empiric risk figures are commonly used, this is not a correct assumption, the frequency of congenital defect rising significantly among the children born to older mothers. Thus, in the Japanese material described by Dr. Schull and myself (1956), congenital defects are two to three times as frequent among the children of mothers over 40 than the children of younger mothers; and this increase has not as yet been shown to be associated with any particular defect or group of defects. In the case of congenital defect, then, truly accurate empiric risk figures should probably be based only on children born subsequent to the birth of the first affected, although the actual correction so introduced will not usually be large.

In the case of Mongolism, one of the most frequently encountered congenital defects, this age effect is especially striking. Thus, among all the siblings of children with Mongolism, the frequency of Mongolism is about 1 per cent. However, among children born subsequent to the birth of a Mongol, the frequency of the condition is about 4 per cent. The latter is the correct empiric risk figure, since it is the subsequent children whom the parents are inquiring about (Böök and Reed, 1950).

An empiric risk figure carries no implications concerning etiology and is, in fact, an expression of ignorance concerning etiology. Where the genesis of a particular trait is understood, one need not rely on empiric risk figures. For instance, consider a very rare, recessively inherited syndrome. As material on this condition accumulates, it

will first become apparent that there is an appreciable recurrence risk. It will also become apparent that there is more consanguineous marriage among the parents of affected individuals than in the population at large. In time, the recurrence risk will be shown to approximate 25 per cent and the data will justify the conclusion that this is a recessively inherited trait. At this point, one can base one's predictions on a specific genetic mechanism.

An important corollary of the fact that empiric risk figures reflect our ignorance as to precise etiology is the conclusion that the application of such figures to the individual case may in reality be quite misleading. Thus, current thought concerning the etiology of congential defect clearly emphasizes the concept of multiple causative factors. Some individuals with such a trait as harelip may owe the condition to a transient disturbance of maternal metabolism during pregnancy or to a pure accident in the complex machinery of development, an accident which has no increased probability of repeating itself. Other such individuals may owe their condition primarily to their genetic constitution. Finally—and I suspect this is the largest group—the trait in some individuals may result from an interaction between features of the intra-uterine environment and the individual's genetic constitution, *i.e.*, the combination of "environmental" factors with a prepared soil. One overall risk figure applied to all these cases will in some instances overestimate the risk, and in other instances underestimate it. One of the really pressing needs in genetic counseling is the development of methods which will permit us to distinguish between these possibilities. Considerable progress has been made towards detecting individuals who are the genetic carriers of various inherited traits (reviews in Neel, 1953; Neel and Schull, 1954; Hsia, 1957). An extension of this same approach to the field of congenital defect may be fruitful, in that some parents might be found to exhibit on close scrutiny sub-clinical findings which would indicate they were the carriers of certain genes responsible for hereditary defect, while other individuals would not exhibit these findings.

The empiric risk figure employed in a genetic counseling problem is at best a tentative figure, subject to revision in the light of future experience. Thus, we have on several occasions been consulted by parents whose first-born has exhibited a very rare constellation of congenital abnormalities. Since empiric risk figures on this specific constellation were lacking, we fell back on the rule of thumb that there is in the neighborhood of a 3 to 5 per cent recurrence risk for most of the carefully studied congenital defects. This general figure, together with other pertinent information, was given the parents as a guide for their thinking. However, it was always emphasized that simple recessive inheritance could not be ruled out, and if they should have the misfortune to have a second child with the same combination of defects, then a revision of the recurrence risk may be in order.

Finally, to round out this presentation, I should state the obvious, that empiric risk figures are no substitute for a careful family history. Such a history will sometimes delineate high risk families, to whom the ordinary figures do not apply.

In summary, then, empiric risk figures are essentially pragmatic probability statements based on accumulated medical statistics. The figure employed for any specific defect undoubtedly encompasses a number of different etiologies. A task confronting human genetics is to learn to distinguish between these etiologies, a development which will put genetic counseling on a sounder basis.

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CHAIRMAN GLASS: The next speaker on the panel is one who, so far as I know, did not start his work in the field of genetics by working on the lower animals, but he has certain other qualifications that render him almost ideal in his position on this panel. If there is anything a heredity counselor needs, I suppose it is tact and good judgment, and I don't know anyone who exhibits continually greater tact and has a greater flair for catching up the ideas that have been bandied back and forth in a discussion and putting them in a nutshell than Nash Herndon. He did it excellently this morning, and we will hear from him again.

PROCEDURES FOR REFERRAL TO HEREDITY COUNSELORS

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THE TERM REFERRAL SHOULD BE interpreted broadly to include all mechanisms whereby the heredity counselor and the patient, or members of his family, come into contact. It may be useful to consider referral procedures in relation to the primary functions of a medical center. Generally speaking, a medical center has three major functions. These are, first, teaching; second, research; third, patient care. Many medical educators rank these functions in importance in the order given.

A teaching service requires a well-balanced variety of problems to provide a flow of suitable material for the purpose of training students and house officers. Most of the material needed for teaching can be provided by the normal flow of patients found on any active pediatric and medical service. This material can be readily utilized by making arrangements for the heredity counselor to attend ward rounds and staff conferences normally held on these services. Conferences with the students and house officers assigned to patients of genetic interest can be used to guide the student in collecting suitable pedigree material and in outlining suitable advice to the patient or his family. This function is particularly valuable in increasing the number of physicians in the community who are able to handle many counseling problems directly, and who will refer the more difficult problems to the specialist in genetics.

Establishing contact with patients needed for research projects can be done in a variety of ways. Usually a method is re-

quired for obtaining an unselected and statistically unbiased series of patients of a type suitable for the research plan. Often this will depend on the establishment of close rapport between the geneticist and the house staff of the teaching hospital. Arrangements should be made with the chief of the proper service for notification on admission of any patient suspected of having the condition selected for study. This should be supplemented by an arrangement with the record librarian to obtain notification concerning all hospital records received bearing the desired diagnosis as these records are received on discharge of the patients. A plan of this type must be implemented by seeing the patients promptly and obtaining the necessary studies, and leaving a consultant's note on the hospital record, and also by conferences with the house officers concerned.

Research problems may also require the collection of information on a series of cases previously seen in one or more hospitals or clinics. As the patients are no longer immediately available, this requires a record search and usually home visits. The technique of conducting survey studies of this type was discussed extensively at the conference on problems and methods in human genetics held at the National Institutes of Health in October of 1953 and published in the *American Journal of Human Genetics* (Neel, 1954; Herndon, 1954; Macklin, 1954). In these studies contact with the patient is usually established by a field worker, and this contact is often made much easier by working through the family physician.

The function of patient care involves all referrals that are initiated by the patient, his physician, or a social agency, and will be unrelated to the research activities of the department. These referrals may be received in several ways. The staff geneticist may receive consultation requests on patients in the hospital or clinic from the attending physician in the usual consulting routine of the hospital. If the geneticist succeeds in demonstrating to his clinical colleagues his usefulness in the management of clinical problems, this consultation service can be expected to become rather heavy. Similar referrals may also be received from practicing physicians whose offices are located outside of the medical center. These referrals are usually made by letter or by telephone. The magnitude of this service depends upon the degree of genetic education of the physicians practicing in the community or area and their awareness of the usefulness and availability of the consulting service. In our experience the bulk of referrals of this type are received from physicians who took courses in medical genetics as students or were house officers in a teaching hospital with a genetics service. Awareness of the usefulness of this service can be stimulated by talks to county medical societies and other medical groups. It is important to maintain an efficient appointment schedule and to report findings and recommendations by letter promptly to the referring physician. The patient should be encouraged to remain under the care of the referring physician, and the consultant should work in cooperation with the referring physician.

Referrals may also be received from various social agencies including welfare departments, health departments, adoption agencies and various private service organizations. These must be based on a mutual understanding between the counselor and the agency concerning the method of referral and the information to be collected and supplied by the agency. This can be made more effective if the counselor will give occasional educational and informational talks to staff meetings of agency workers and to other meetings of social workers, public health nurses and other personnel concerned. In dealing with agencies, the problem of privileged communication must be handled with care. The counselor may submit a report to the agency only if he has written permission from the patient or his family to do so. The counselor must be

careful to observe the pattern of medical ethics and the legal requirements for transmission of information to non-medical personnel. The patient will usually regard the counselor as equivalent to a physician in terms of doctor-patient relationships, and the counselor must avoid any action that could possibly be construed as malpractice. In this connection it is most important to keep an exact record of the advice given to the patient verbally and to keep records of all correspondence. Even with agency-referred patients, it seems advisable to work with the patient's family physician if this is at all possible or to suggest that he obtan a physician.

In addition to patients referred by others, some patients will refer themselves. The existence of an heredity clinic is often publicized in newspaper or magazine articles, and numerous mail inquiries are often received after such publicity. All letters so received should be answered, but much caution and tact is required. Some of these will be requests for general information, for example, students writing term papers, and these may usually be handled by a routine letter or by sending appropriate pamphlets. Requests for information on specific diseases or specific family problems are potentially dangerous and must be handled with care. In our experience information given in such letters is often erroneous and could lead to improper advice if one attempted to supply genetic counsel upon such inadequate information. It is surprising how often such letters give incorrect diagnostic information, apparently resulting from misunderstanding or misinterpretation of verbal information received from physicians. Giving genetic advice on the basis of an unsupported letter should be avoided. Every effort should be made to induce the patient to consult his family physician and obtain referral through this source, or to have the patient visit the clinic for both diagnostic examination and genetic study. It is often possible to give suitable advice to a physician for transmission to a patient that cannot be seen in person, but this should be based only upon accurate diagnostic and pedigree information collected by the referring physician.

A final type of referral is that which may be received from a court in medicolegal cases. These must also be handled with care to meet the legal requirements for blood group testing. Arrangements for blood testing are usually made by attorneys and upon court order. Care must be taken to maintain the legally required chain of evidence. The individuals concerned must be properly identified, and preferably the opposing parties to the action should identify each other in the presence of the geneticist. Reports with proper interpretation should be sent direct to the clerk of the court concerned, with copies going to the attorneys representing both parties.

In summary, patients may be referred to the genetic counselor in many ways and for many purposes. In general, it is advisable to work with the patient's physician if this is at all possible. Due care must be taken to avoid errors that can occur as a result of incomplete diagnostic or inaccurate pedigree information, and careful record keeping and reporting to the proper physician or agency is essential.

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CHAIRMAN GLASS: Our next speaker, Dr. Clarke Fraser of McGill University, is equally well known to us for his work on human genetics and his work on mice. I don't know whether the mice led him to the men, or the men led him to the mice, but of mice and men, anyway, his career has been made. He's going to talk about "The Types of Problems of Heredity Counselors."

TYPES OF PROBLEMS PRESENTED TO GENETIC COUNSELORS

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MY DISCUSSION WILL BE LIMITED to what kinds of questions genetic counselors are required to answer, how many cases they may expect to deal with, and where the questions come from. In order to get some information to talk about, I sent a rather rough-and-ready questionnaire to some of my counseling friends, who have been very generous in their response, and whom I would like to thank for their cooperation. The object was simply to get some impressions of the sort of case-load carried by counseling centers, and no claims to statistical validity are made. The questions dealt with the number of cases referred per month, what proportion were referred from hospital wards, practitioners, or came directly, what categories of questions were asked, and the five most frequent conditions encountered.

The first question dealt with the number of cases per month referred for genetic counseling. The answers would depend somewhat on the method of classification; some correspondents might include referrals for zygosity diagnosis in twins, for instance, and others might not. The answers ranged from 1 to 40 referrals per month. This volume might be expected to rise somewhat as the benefits of genetic counseling become more widely appreciated. However, it seems unlikely that counseling centers will ever become self-supporting on the basis of income from fees. (This is one of the problems of genetic counselors.) No information concerning fees was gathered by the questionnaire, but it seems from personal conversation that fees are not usually charged, at present.

The sources of referrals would be expected to vary widely according to the organization of the particular center, and so they did. Counselors associated with medical centers received anywhere from 20 to 80 per cent of their referrals from the hospital wards. The proportion of cases referred from physicians varied from 10 to 80 per cent, and the proportion that came directly to the counselor varied from 0 to 90 per cent. Some centers actively discourage the direct approach, and one center insists that referrals shall be through a practitioner or hospital. Our department does not employ such a hard-and-fast rule, but we believe that in genetic counseling, as with any medical specialty, the practice of referring cases through medical sources should be encouraged. For one thing, it is easier to get reliable medical information about cases referred in this way, and, for another, the counselor is given added prestige in the eyes of the patient by this approach. Additional sources of referrals are institutions and agencies, but referrals from

these sources appear to be in the minority. Several centers, including ours, try to avoid giving advice by mail, although sometimes the person requesting information is so remotely situated that there seems to be no alternative. I think several of you have had experience recently with a request from New Zealand for advice as to a contemplated cousin marriage. This person apparently also conducted a survey of genetic counselors—it would be interesting to see how much variety there was in the replies.

The questions asked of the counselor could be grouped in a number of categories. The most frequent type of question seems to deal with whether parents should have a baby, the problem arising either because they had already had a child with some disease of presumed or actual familial tendency, or because some such disease was present in one of the parents themselves or in some more distant relative. The next most frequent type of question deals with the desirability of a contemplated marriage, either because of consanguinity or some genetic disease in one of the families involved. Some cases are referred for an opinion as to the genetic suitability of an adoption procedure, some for an interpretation of the cause of a child's illness or defect (apart from eugenic considerations), some for an opinion as to the chances of a sibling or other relative of an affected person becoming affected in the future, and a few for other reasons such as paternity disputes, zygosity diagnosis in twins, dermatoglyphic diagnosis of Mongolism, and diagnosis of rare, obscure diseases. We have had, as yet, no experience with artificial insemination, although the procedure has been discussed in a few cases, and we have, as yet, had no requests for DNA transformations, although we are expecting one any day.

We did have quite a number of requests to diagnose sex before birth after the Richardson saliva test became known, and I might mention, incidentally, that although one could make the diagnosis with better than 90 per cent accuracy, a few cases that were wrong were so upsetting to the parents that they far outweighed the minor benefits of the ones that were right, and we no longer provide this service.

The specific conditions involved were of such great variety that there is little point in discussing them in detail. "Congenital malformation" was the group most frequently mentioned in the questionnaire. Others that appeared several times were neuropsychiatric conditions, consanguinity, Negro-white skin color, Mongolism and Rh trouble. The type of condition referred would be expected to depend somewhat on the interests and situation of the counselor. Dr. Kallmann would no doubt find a high proportion of his referrals were neuropsychiatric problems, and Dr. Walker almost certainly gets a lot of Mongoloid imbeciles referred to her. Hemorrhagic diatheses form a large portion of the cases referred to Dr. Herndon, because of his hematological colleagues' interest in clotting mechanisms. Unlike some centers, we are hardly ever bothered with skin color problems, and the hematologist handles cases of Rh disease and disputed paternity. Most of the counselors questioned reported a "miscellaneous" category including a wide variety of rare but relatively clear-cut diseases, too numerous to mention here, and it would seem probable that a large part of counseling practice deals with cases of this sort.

I shall be interested to hear how well, or badly, these rough impressions of the nature of a counselor's practice correspond with those of other members of this group.

CHAIRMAN GLASS: I'm certainly glad that this question of the support—the financial support—of heredity counseling and the question of fees is coming up. I hope that it will be discussed more fully.

I just want to say at the moment that, during the past year and a half, I would have had to employ an extra secretary to keep up with the mail inquiries about the genetic hazards of various kinds of radiation which have piled up on my desk. And, in this regard, I also feel it's a nice little courtesy when the author encloses a self-addressed envelope with a three-cent stamp on it, but I can't help feeling a little hurt when he encloses a dollar.

CHAIRMAN GLASS: Our next paper is "Types of Advice Given by Heredity Counselors," to be given by Dr. Franz J. Kallmann. Dr. Kallmann is one who certainly needs no introduction to any audience like this. Let me just say that, in my own opinion, one of the reasons — and not the least of the reasons — for the decline of human genetics in Germany and Austria during the 30's and 40's was brought about by Dr. Kallmann's transfer to this country.

TYPES OF ADVICE GIVEN BY HEREDITY COUNSELORS

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HAVING HAD THE PRIVILEGE OF KNOWING the program chairman for many years, I am sure that his decision to save the least conformable topic of this interesting symposium for the very last, like fireworks, was an act of prudence rather than a reflection of hidden sentiments. He understands that with the types of advice given in heredity clinics depending primarily on the functional character of the clinic, the nature of the problems presented, and the professional qualifications of the counselors available, there can be no uniformity in this area. It is also clear that, while the unfolding of some inevitable differences of opinion may be both sparkling and noisy, the general effect of such fireworks is harmless and good fun.

In other words, even if I do not always see eye to eye with every member of this panel on some psychiatric issues, we are still good friends dedicated to a common cause. More specifically, we are all agreed that heredity counseling is an important and rather exacting task which requires a high degree of proficiency and must be learned. In the last analysis, the type of advice given can never be better than the level of professional competence of the counselor who is giving it. It is therefore doubly regrettable, as has been stressed by Herndon (3) and others (6,8,14), that although counseling in medical genetics is part of a preventive public health scheme, our training programs have yet to prepare future heredity counselors for activity in this vital sector of public health work.

Under these circumstances, the simplest way of defining the kind of advice given by a heredity counselor would be to paraphrase Calvin Coolidge's account of a sermon on sin. Just as Coolidge's preacher

was *agin it*, so we might say that genetic counseling should be *free of it*—at least as much as possible.

While there are major and minor sins in operating a unit for providing advice in matters of human heredity, this distinction may vary according to whether a counselor's concern is with pre-marital, marital, pre-parenthood or pre-adoption problems. If the contact is directly with the persons seeking counsel, rather than with their regular physician or a public health agency, the least pardonable sins in counseling work are violations of one of the following rules:

1. The responsibility of counseling should be delegated only to personnel who are professionally competent, tactful, and mature enough to empathize with persons in need of guidance. Such workers will always be mindful of the fact that as members of a health service team, they are expected to understand the age-old medical principle of *nil nocere*. People in whom fears of a crippling or fatal disease have been instilled or aggravated by thoughtless or strenuously realistic remarks of an inexperienced counselor are likely to misinterpret even the most logical kind of advice and may become as distressed and debilitated as if they were actually afflicted with the disease they dread (2,7,15). It makes little difference whether one has cancer or is mortally afraid of it.

2. Inasmuch as specific counseling problems of clinical genetics require evaluation in terms of the total health and adjustment levels of a given family, they should never be dealt with in an *impersonal* way. Mail order methods may be profitable in other fields of endeavor but not in counseling work. By correspondence it is difficult to form an opinion regarding the predictable stability of the home which a young woman will share with her future husband, after a psychotic episode, or into which a child with a calculable morbidity risk will be born.

3. If the genetic counseling problem presented concerns a clearly pathological trait, it is essential to bear in mind that the potential health risks connected with marriage on the one hand, and with parenthood, on the other, may differ so considerably as to call for opposite decisions and entirely different supportive reorientation designs (4,5,6). Whatever the preferential pattern of conduct with respect to the two issues may be, they are to be *kept apart* in most areas of genetic guidance and should not be subject to biased value judgments on the part of the counselor.

4. Persons requesting genetic advice cannot always be presumed to be capable of making a realistic decision as to the choice of a mate, or the advisability of parenthood, without support in the form of directive guidance and encouragement. As is true in recommending any restrictive regimen, people coming to heredity clinics may have to be told *how* to adjust, for instance, to a childless marriage or a family deliberately limited in size.

It is undeniable that reality enforcement without guidance may create anxiety, conflict and ill health (2,7,10) and, therefore, is inconsistent with accepted standards of medical ethics as applied to the work of related service professions in the field of public health (14,15). Hence it would seem inappropriate to withhold tension-relieving support from indecisive and perplexed people when it lies within our power to provide such help in a genetic counseling situation. It is possible, of course, that counseling problems of this kind are particularly common in a genetics department connected with a psychiatric institute. It is safe to assume, however, that similar problems are encountered in heredity clinics specializing in other areas of clinical genetics.

In line with the four rules for *counseling without sin*, every heredity counselor should be able to determine when he cannot refrain from giving "directions as to what clients should do" or when he cannot rely on the diagnosis presented to him (11,12,

13). Even in those centers where genetic counseling is merely regarded as "a type of social work carried out by the geneticist or family physician" (13), its main objectives will not always be confined to promoting the happiness of married couples. Apart from creating "sub-specialty barriers" within an important discipline that has much need of teamwork and cooperation (2,15), such constrictive formulations may cause us to lose sight of the over-all mission of medical genetics in the field of public health.

To illustrate the willingness of guidance-seeking people to cooperate with a *personalized counseling program*, I should like to quote from a rather typical exchange of correspondence. A few weeks ago, we received an airmail letter from a young woman in Georgia, which read in part: "I am engaged to marry a young man who has a history of abnormality in his family. His parents are alcoholics, and of his four brothers and sisters three are feebleminded and unable to care for themselves. . . . I would like to have children after we are married, but would rather adopt them than have any ourselves if they were likely to be as unfortunate as his brothers and sisters. . . . Would you please let me know what your opinion is in the near future, as we are planning to be married soon and this problem is causing us a great deal of concern. . . ."

Following our usual procedure, we advised the young lady that her problem was too important to be dealt with by mail. Among other things, it was suggested that she and her fiancé come to see us. Her reply speaks for itself: ". . . . We have decided to take your advice and postpone any decision as to whether or not to have children until we can consult with you. Circumstances prevent our being able to come to New York at this time, but we are hopeful that by the first of the year it may be possible. We will contact you again at that time. Thank you for your courtesy" —a closing sentiment which echoes my own at this moment.

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CHAIRMAN GLASS: The second speaker on this same topic, "Types of Advice Given by Heredity Counselors," is Dr. Sheldon Reed. Like Dr. Fraser, Dr. Reed has shifted from mice to *Drosophila* to human genetics, without entirely forsaking the love for experimental work with which he began. I think his work in counseling at the Dight Institute, of which he has been head now for a number of years, pays great tribute to his interest in problems of this field.

As many of you know, he has written a book in which he has dealt with problems of this kind and has endeavored to make clear to physicians with not a great deal of genetic background what approach might be taken in answer to many of the problems brought before them. So we will listen with great interest to Dr. Reed.

TYPES OF ADVICE GIVEN BY HEREDITY COUNSELORS

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DURING THE PAST TEN YEARS Dr. Ray C. Anderson, Elving Anderson and I have recorded 1,778 counseling cases as of July 1, 1957. This number comes from the daily log which we keep and which affords a starting point for follow-up contacts to determine the results, if any, of the counseling. Such contacts have been made sporadically in the past. It would be valuable to make a careful, systematic study of the first 1,000 cases as they are now old enough to permit a correlation of the clients' statements with their reproductive behavior subsequent to the counseling.

This record of counseling represents a great many hours given freely to strangers for which you expect nothing in return except your own satisfaction that you have done your best to help them solve their problems.

It would be very gratifying if these cases had all been correctly handled and the counseling carried out under ideal conditions. Obviously, such could not have been the case, nor do I know of any center where genetic counseling is entirely satisfactory. The reasons for the less than perfect counseling techniques are many and are responsible for the less than perfect performances in any area involving personal relationships and social work.

The large number of counseling cases mentioned above represents a general genetic counseling practice which could be expected to come to any person identified as being experienced in human genetics. Generally, the clients do not expect nor want very much beyond the genetic information, *and an understanding of it,* for which they have been referred by their physician, frequently an obstetrician. Of course it would be highly desirable if the counselor could have had several years of practice in obstetrics, pediatrics, psychiatry and hematology, to name a few of the pertinent disciplines, in order to gain a solid background in all fields. Probably the best that can be hoped for, however, is that he might have an M.D., in addition to his Ph.D. in genetics. These fields are all important in counseling, and there are many other ones which would be equally useful, such as legal training and social work. I assure you that training in all these disci-

plines and others would be most helpful in answering the questions posed in general genetic counseling. As no one could ever qualify as an expert in all these areas, genetic counseling will always be somewhat imperfect. Furthermore, if a person did qualify in all the most important areas, he would have reached a pinnacle of professionalism which would make him the world's worst genetic counselor. Professionalism leads to a kind of aloofness and austerity that expects automatic acceptance of the pronouncements given. As these expectations may exceed actualities, bitterness may result and the counseling has failed. As the old gag goes, "You can always tell a Harvard man but you can't tell him much."

What you can tell a person or couple depends upon the situation, which is practically always unique. If you say to the couple, as many physicians have said, "You must not have any more children," there is a good chance that the couple will resent the statement and look elsewhere for a less dogmatic presentation of the situation. Conversely, if you again rest upon authority and tell the couple that there is no danger of a repetition of an abnormality, they may doubt the statement with resulting frustration. It would seem clear from the whole of our cultural experience that people do not wish to be *told* how many children they can have. This is the reason that most genetic counselors emphasize that decisions regarding reproduction must be made by the couples themselves. Furthermore, I can assure you from both my personal and professional experience that the couple is not prepared to make their decision about subsequent reproductive intentions at the time they get the genetic counseling. They *will* take their time and think over what they have learned, or thought they learned.

There is a fundamental difference between psychiatric and genetic counseling. The psychiatrist can expect and demand a number of sessions with the patient. The genetic counselor cannot demand this and usually expects to have only one meeting with the clients. If there are two or even three meetings with the couple it often means that a poor job of teaching was done at the first meeting. Genetic counseling is a one-shot proposition, most of the time. Subsequent to the birth of a child a couple may reappear for a further evaluation of the situation.

The experience at the Dight Institute is the same as what seems to have occurred in Denmark at Professor Kemp's Institute of Human Genetics. The proportion of personal contacts with the people involved is diminishing. The proportion of phone and mail contacts with the client's physician is increasing. Phone and mail contacts are not satisfactory methods of counseling and, knowing this, some of the physicians refer the couple to the counseling center, but some do not. It is clear that the main body of counseling in medical genetics in the future will be done by physicians not located at counseling centers. This should be obvious. There are many thousands of families who have questions about human genetics. They're not located anywhere near a counseling center and have never heard that such exist, and, naturally, they ask their family physician whatever question they have in mind. The eventual remedy, of course, for the difficulty here is better training for the physician in human genetics so that he can do adequately the bulk of the genetic counseling, which is coming to him already, and which in many cases he does not do adequately now.

The question is still before us as to what to tell the couples that do come to the Dight Institute for counseling. While we cannot order them to produce a particular number of children related to the gravity of their situation, we can guide them to some approximate understanding of what the risk actually is. This is a tough job in itself, as the clients do not usually have much comprehension of probability even in the simplest penny-tossing form. If the

risk picture can be satisfactorily transmitted to the clients, they will eventually try to fit their reproductive behavior to it. The means by which they do this will be influenced by the cultural and religious pattern in which they were reared. It is not likely that the genetic counselor can change these attitudes very greatly with the one shot he has. Furthermore, the clients in general know about the techniques, and only once in my experience has any client thought that I could personally fix her up with the changes that she wanted to take place. Most of them realize that this function obviously belongs to somebody else. Reproductive attitudes are established early in life and modified only over a long period of time. If the genetic counselor attempts to sell any particular reproductive attitude too vigorously, he will certainly be rebuffed. Even the obstetrician cannot explore his patient's mind on the subject of reproductive attitudes extensively at the first meeting.

In conclusion, it should be clear that to me the people who come for genetic counseling are clients and not patients. They are just as normal as the clients of a lawyer or social worker, or perhaps more so because, in general, they are fairly literate, or they would not know about you or seek advice from you. They come for information which they hope will relieve their anxieties about the future. Fortunately, the information obtained almost always does seem to diminish their fears and stabilize their thinking. They very frequently ask: Is there a chance that I can have any normal children? The chances may be 97 per cent that the next child will be normal, using risk figures for some of these common indeterminate risks that Dr. Neel has mentioned. The presentation of genetic information is the primary function of the genetic counselor. The presentation must be compassionate, clear, relaxed, and without a sales pitch. You will know whether you have succeeded or not as a result of the completely voluntary messages that come in from the clients some years after the counseling. You learn that in many cases, at least, your efforts were not in vain.

DISCUSSION

CHAIRMAN GLASS: If I understand Dr. Reed correctly, it seems that the genetic counselor is somewhere about midway in the spectrum between the radiologist and the psychoanalyst. When the radiologists approach the problem that has been before them more and more frequently in the last two or three years about the dangers of radiation, their answer to the person seeking advice is "Trust your doctor. Do what the doctor says is advisable. Just listen to him. He knows there's a risk, a calculated risk. You take the doctor's word."

At the other extreme, we have the psychoanalyst, who doesn't tell the patient anything but just listens to the patient while he reveals himself. And, in between, we have the genetic counselor, who is not going to be so extreme as the radiologist, who will try to present the facts to the client but who is never going to admit a second interview, and certainly, by no means, to allow the client to recline on a couch while pouring out his trouble. Is that correct?

DR. REED: It's very imaginative, at any rate.

CHAIRMAN GLASS: We come now to the discussants, Clarence P. Oliver, of the Department of Zoology, University of Texas; Harold Falls, University Hospital, University of Michigan; and Dr. William J. Schull, of the Institute of Human Genetics, University of Michigan.

I just want to say, in introducing Dr. Oliver, that—well—I don't usually call him Dr. Oliver. I call him Pete. We were graduate students together, and I'll let you in on a little secret now.

My admiration for him knows no bounds.

As a younger student, I knew of times when he was working so late at night X-raying fruit flies and analyzing the results, in those days when we were just beginning to learn what radiation would do to genes, that he would stretch out on a lab table and go sound asleep night after night and be waked up by the night watchman on his rounds. I think maybe his back is still a little stiff from sleeping on those lab tables; I don't know. But that's the devotion to his work that has characterized him over all these years.

DR. CLARENCE P. OLIVER: In most of the statements that have been made by the speakers, there's very little controversial that we can take up, and they have done the job so well that I rather hesitate to make many comments. But I do want to be certain that some things have not been misunderstood, or will not be misunderstood, and I want to bring out, maybe, one other point that has not been discussed.

I'd like, first of all, to refer to Dr. Dice's paper in which he suggested that there be accurate diagnoses, including the diagnosis of normalcy for those who are reported to be normal. Actually, in studying human genetics, accuracy is extremely important. You will find, if you are working with a characteristic which is not present very early in life, that the proband will probabaly know more about her mother than about her sister, and certainly more about her sister than about some distant relative. It is also true that she will know more about her father than about her brother. You do find occasionally individuals who are classified as normal, not only by the proband with whom you begin your study, but also by other relatives. And yet when you go to the individual to verify or confirm this normalcy, you find that the individual is not normal.

I know one case of breast cancer in which a woman had had both breasts removed—mastectomy—and none of her sisters, none of her nieces, knew anything about this at all. She had kept it quiet from everyone, but she did give the information to us, and we were able to confirm this by going to the hospital records.

I would like to make a statement as well about a point in Dr. Neel's paper which does not differ from his, you understand, but it's something that I had wanted to say this morning and was not able to do so. That involves the impossibility of recognizing individuals who have a particular genotype and who thereby carry the potentiality to develop a particular phenotype in time.

It would seem obvious to most people who have worked with experimental genetics that you can get a mimic of a hereditary condition, the mimic resulting from some environmental factor, and the mimic will not necessarily be identical with the hereditary type. But the fact that you have some slight variation is not in itself evidence that you are dealing with something non-hereditary. Even when you induce mutations, that is, gene changes as we describe them, you will not necessarily get the same phenotype in the second mutation that you got in the first mutation. You may describe them as exactly the same, because your eye is accustomed to seeing some visible variants, and it's the first characteristic that you recognize.

Quite often you will find some new variation intermediate with respect to two hereditary traits, both recessively inherited, and both involving primarily a particular part of the body. This variability of traits is something that we need to find out more about in human genetics, if we want to make good use of family histories in working out the data for use in counseling.

I believe that the speakers today recognize the need of following up, or at least answering, letters that come to them, even though all of us recognize that these letters will not ordinarily give us sufficient information about the trait involved. You want to get accurate information when you can, but when you cannot, you still may want to—and you should—give a tactful answer to the person who writes the letters.

I believe that should be done, because I feel that most of the people who write in for ininformation have a problem disturbing them. As one human being to another, if for no other reason, you should do the best you can to relieve them from the anguish, or tell them exactly what is known about the possibility of this trait developing.

There is something else, too. Sometimes a person writes to a counselor, that person living all the way across the country from the

counselor. The letter is sent for a particular reason, and I think an example will be the best way for me to explain it to you.

One individual first wrote a letter and then, eventually, came in to talk about his problem. After the discussion he was asked why he did not to go to a geneticist living close to him, although not in the same city, to get his information. His answer was that if the people in his home area found out about the complication he was involved in, he would be socially ostracized and economically ruined. Therefore, he did not dare go to someone who could answer his question but who also lived close by, because there was a possibility that the news would leak out. So he spent considerable money to talk to someone at a distance.

I want to mention something about finances, too. I certainly am not going to plead for charging of fees. I don't believe in it. It's perfectly justifiable if you are a physician examining the individual for medical data; but in so far as genetic counseling is concerned, I do not believe in charging fees. I would not want to attack anybody else having a different belief.

That statement was answered once by someone who said that I preferred to be a gentleman rather than a worker, and that may be it. I don't know. Actually, I just feel that most of the people who come to us for information are not able to pay fees, and that if we in genetic counseling begin to charge fees many will look upon us more as professional individuals and not as human beings. I apologize to anyone to whom that may sound as if I'm saying they are not human because they are professional. I hope you will see what I mean; that it is essential that you treat these individuals as fellow men who have problems, for they want someone to whom they can turn in confidence to discuss the problems and to get some honest advice about the possibilities, even though you can't keep them from developing the trait because medical knowledge has not progressed that far.

There has been nothing said about training. It's doubtful that anyone could set up a program for training in genetic counseling. Some individuals might conceivably be able to do it, but most of us could not. It certainly is true that not everyone could be trained to become a genetic counselor. There are excellent geneticists who could not learn to act as counselors even though they know all of the subject matter in human genetics. There are physicians, of course, who are accustomed to counseling, but they may lack sufficient knowledge of genetics, and many of them would not go into genetic counseling. Possibly some of those could be trained to become genetic counselors. You do need some means to train individuals in genetics, if they do not know genetics, and to give them a broader knowledge in human genetics if they already know basic genetics.

That can be done only if certain schools where individuals who can give this training are located will develop a program of training in human genetics. That means as well that the school ordinarily will have to get funds from the outside for that purpose. There are possible sources for those funds, but at present there would not be a large amount available for any one group.

CHAIRMAN GLASS: Dr. Falls, you're next.

DR. HAROLD FALLS: American medicine has experienced cycles of specific interest and now, after a rather long preoccupation with mechanical gadgets and instrumentation, has again turned to a consideration of *the individual as a whole person*. The physician, in such a consideration, must necessarily investigate the patient's economic status, social responsibilities, social attributes, level of education, reaction of the psyche to the illness and particularly the hereditary make-up. The patient and his disease must therefore, be carefully evaluated in light of the combined influence of that individual's environment and hereditary make-up. The human geneticist and/or counselor, perhaps better than any other discipline, needs to employ this careful consideration of the individual *as a whole person*. In order to give a satisfactory genetic prognosis, the counselor requires the following aids: (1) careful and accurate diagnosis, (2) meticulous study of the specific individual's family and (3) a thorough knowledge of the medical and hereditary literature dealing with the specific trait or traits being studied. It is not always possible to fulfill these requisites necessary to the giving of a genetic prognosis. The counselor, therefore should possess that most important attribute—honesty. The limita-

tions of available knowledge and difficulties of accurate diagnosis should be admitted freely and demonstrated to the inquiring individual. Recent attempts at classification of specific disease entities have uncovered the fact that the medical profession is just beginning to explore the field of the minutiae of differential diagnosis. The difficulty of accurately classifying the so-called achondroplasias was very well emphasized this morning in Dr. Warkany's excellent presentation. To further illustrate, the ophthalmologist has learned to consider the term *retinitis pigmentosa* as a clinical wastepaper-basket type of diagnosis since there are now recognized seven different known hereditary modes of transmission of this interesting ophthalmoscopic picture. Drs. Neel, Dice, and Herndon have called attention to the frequency of the so-called "carrier-states." This subject was also alluded to by Dr. Warkany when he spoke of "signs and symptoms" of the traits present in other siblings and relatives of his patients. In such "carrier-states" the individual heterozygous for a "recessive" gene may occasionally or even constantly exhibit minimal or mild effects of the gene in contrast to the more severe or extensive manifestations of the homozygous state of the gene. Such findings merely lend emphasis to the previously made statement that the genetic counselor must meticulously study and individualize the entire family of the afflicted person before making any conclusions as to the mode of the gene transmission. It is to be admitted, however, that genetic prognosis can be made occasionally even though a definite diagnosis cannot be arrived at. This is particularly true if a careful pedigree is available. Before leaving the subject of diagnosis, I should like to digress a moment to speak of a fallacy and tendency exhibited by physicians in anticipating an all or none effect of a specific gene. These same physicians, however, do not expect a textbook picture in each of a hundred cases of measles but rather anticipate differences in the manifestations and the course of the disease. The geneticist must educate the physician to realize that no one gene acts alone but rather experiences a very complex interaction in the gene milieux of the affected individual. Since this gene composition varies greatly in every individual (except monozygous twins), significant variations in both expressivity and penetrance of the gene should be expected. The textbook picture expression of a gene effect therefore is seldom observed; rather variation becomes the rule. These differences in expression of many disease traits are perhaps further accentuated or brought about by differences in the environment of the affected individuals.

The most important requisite of any genetic counselor is the possession of a high degree of common sense or, to put it more bluntly, just plain "horse-sense." The effect of any specific trait on an individual's ability to become a useful member of society and in addition upon the mental status and social standing of that individual's family must be weighed carefully in giving genetic advice. The singular fact that such prospective parents actually seek genetic prognostication indicates a greater degree of intelligence, social and moral responsibility on their part than is true of a large proportion of our population. Such parents, perhaps, should actually be encouraged to have children (anticipating transmission of superior qualities) providing the gene to be transmitted does not impose too serious a handicap on the affected child.

In respect to lethal traits (Tay-Sachs disease, for example) the counselor, if convinced that the parents possess better than average intelligence and social responsibility and particularly if the prospective parents could tolerate the psychic, economic, and physical stress, may advise them to continue trying until they secure a normal child. This is in contra-distinction to their adopting a child of even greater unknown qualities. Such advice of course presupposes a most thorough insight into the mental and physical character of the parents seldom achieved by a counselor in the course of the usual interview.

To further emphasize the importance of considering the *individual as a whole,* it is mandatory that the counselor delve into a careful consideration of the influence of the maternal environment on the afflicted offspring. In this respect it is necessary that a careful history of the maternal health during the pregnancy be inquired into since it is well known that viral and other noxious environmental agents can effect changes in the fetus which closely simulate the product of a noxious gene action

(phenocopy). Several of the acute viral exanthemata may not manifest themselves in the pregnant female who has sufficient immunity to protect herself but not sufficient immunity to prevent the fetus from the deleterious action of the virus. Thus, the counselor must know the probability and time of exposure of the pregnant woman in order to evaluate the possibility of noxious intrauterine viral action on the child.

Maternal hereditary states, such as diabetes, RH factor, ABO factors, anatomical defects and others must also be carefully considered by the counselor. A diabetic mother may give birth to successive obese infants while an RH or ABO incompatibility may likewise lead to successive siblings exhibiting erythroblastosis. Breech deliveries have been known to occur more frequently in specific females and in particular families. Finally, mutation as an important cause of disease must always be kept uppermost in the mind of the counselor.

In conclusion I should like to say a few words about treatment of genetic disease states. I am quite optimistic and believe that we will be able to ameliorate and prevent the ravages of many of the metabolic entities which seem to plague our elderly individuals. Early recognition and diagnosis of such metabolic entities as hypertension, arteriosclerosis, diabetes, arthritis, etc., before they reach the clinical level through careful study of all members of known afflicted families and through better provocative tests is to be anticipated. The early detection of individuals destined to be afflicted with these disease states will make it possible for medicine to ameliorate and perhaps even control the disease.

DR. FRASER: I'd like to raise a question about the eugenic aspects of counseling. Dr. Falls has said if the parents could take it, he would tell the parents of a child with a recessive lethal disease to go ahead and have their next child. I'd like to ask him what he thinks about the fact that our advice will act in the direction of increasing the frequency of the gene for that disease. We all do this, I suppose, when we tell the parents of a child with harelip or other condition with a partly genetic basis but low recurrence risk that the outlook for future children is not bad.

DR. FALLS: Dr. Muller has estimated that each of us carry at least eight rare hidden genes.

I am aware that in telling such parents to go ahead and have children (anticipating a clinically normal individual but possibly a heterozygote-genotypically) that they will further increase this pool of rare recessive genes in the general population. I cannot believe, however, that contrary advice, if followed, would materially lessen our recessive gene burden, particularly in the light of known constantly recurring mutation.

It has been my experience that many individuals after acquiring an understanding of the empiric risks through genetic counsel not infrequently decide to gamble on having their own child. Certainly no counselor has the legal right to say "thou shall not have a child."

DR. FRASER: I quite agree.

DR. FALLS: While speaking about legal responsibility, I should like to warn all counselors to keep written copies of their opinions on file. In giving genetic information through the mail, I believe it is legally expedient to quote genetic textbooks freely and to avoid personal opinions. I am not certain to what extent the counselor can be held legally responsible for a mistaken prognosis, but this possibility should be kept constantly in mind.

CHAIRMAN GLASS: Our third discussant is Dr. Schull, the co-author with Dr. Neel of a recently published book *Human Heredity*.

DR. WILLIAM J. SCHULL: The role of third discussant at a meeting such as this is an unhappy one, since the discussant is expected to have a measure of clairvoyance that I don't possess. One is expected to foresee manuscript changes which take a person from Texas to Georgia, and what previous discussants may elect to say. The easy way out in these circumstances is to tell jokes, but, unhappily, Joe Miller was not one of my ancestors. The net result was that in attempting to determine my contribution to this meeting I went through a series of mental peregrinations that would have done credit to Walter Mitty. One moment I had visions of myself in the role of devil's advocate, and the next moment I saw myself voicing unobjectionable platitudes. Only time will tell what the final casting was.

Dr. Oliver has mentioned fees, and, perhaps, our experience at Michigan will be enlightening. At Michigan we do charge for our genetic counseling. I should qualify this by saying that we charge, indirectly, for a portion of our genetic counseling. Individuals who seek guidance from us at the University of Michigan — and this is personal interviews that I'm speaking of — either come to us from within the hospital on a referred basis, in which case there is no charge for our services, or they can come to the out-patient clinics to be seen on the heredity service. In the latter instance they pay the entering fee that is charged every individual who seeks some sort of help through the out-patient clinic, so, in a sense, the individual is charged for our services. Personally, I do not find this especially reprehensible. It has been our experience that though the old adage goes that one should not look a gift horse in the mouth, most persons scrutinize the gift horse more carefully than something they have paid for. I sincerely believe we obtain a rapport with the patient who pays for counseling that one does not obtain when the patient is seen without charge.

The area that I thought I might address myself to, without challenge, was the estimation of empiric risks. The statistician is probably happiest, as you know, when he's the only statistician in a group. But I see in front of me Dr. Howard Levine, so I shall have to make my statements cautiously.

Almost without exception, the designs we have used—and I do injustice to the word "designs"—to obtain empiric risks are naive statistically. One does not see multistage sampling used nor any of the other recent advances in sampling theory. What is worse, one cannot generally characterize the population from which a sample, given in the literature, was presumably drawn. Now, we all know, and I think we all appreciate, that in empiric risks we are invariably sampling from a mixed population. The population contains matings with high risk, with low risk, and possibly others. We have no notion as to what proportions of the various classes are in this mixed population, but in many cases we do have sufficient information about concomitant variables so that these, at least, could be taken into account when we attempt to obtain useful empiric risks. As Dr. Neel has said, empiric risks are a measure of our ignorance; but there are degrees of ignorance and I'm sure we can refine the empiric risk figures which we use by sharpening the definitions of the populations from which we are sampling, and by employing more informative sampling designs.

Before we can evaluate the importance of empiric risks or determine where greater emphasis should be placed in securing such figures, we should have some notion as to what these risks mean to the individual who is counseled. More specifically we should know when the individual who seeks guidance decides that a risk is too great. If we knew this, then we could and should place emphasis on securing the best possible figures when the risk falls within this decision-making area. At other levels the empiric risk could vary by an order or even two orders of magnitude and would be of no concern to the individual. Thus, I am sure that most people who seek genetic advice and who are presented, say, with an empiric risk of one in a hundred, would make the same decision on the basis of this risk as they would if their chances were two in a hundred. This difference, which is small in their eyes, although it represents actually a doubling of the risk, almost certainly plays no major role in the ultimate decision which they reach. But I do believe that by the time the risk approaches one in ten, then they begin to hesitate, and by the time the risk reaches one in two, they may decide not to have children. We should concentrate, therefore, on this area of transition where the empiric risk is taken into account in arriving at a decision. Within this critical zone we perform a disservice when we can not provide accurate figures.

I would like to comment just briefly on the type of advice which is given. Dr. Kallmann set down four rules that one should operate by, rules which I think are very well taken. There was one instance, however, where I, with Dr. Kallmann's permission, would like to make a small change. He said, if I recall correctly, that genetic counsel should never be given in an impersonal way. If he would permit me, I would like to change this to read: genetic advice should be given in a compassionate fashion. Impersonal means without reference to self, as I understand its use here, so that if

advice is not impersonal, it must be personal. If it's personal, it must be subjective, and I doubt that two counselors would proffer the same advice. Since many of the individuals who seek advice shop for it, they are apt to be led into an area of confusion because of differences of opinion, which makes it impossible for them to arrive at a decision.

One other comment—and this I owe to Dr. Warkany who said, "Do we actually need counseling centers in Bloody Creek, Kentucky?" As we are aware, genetic counseling has erupted with a vengeance in the last several years, and I often wonder if we are not being stampeded into attempting to establish many counseling centers when we don't have the personnel to man adequately the ones that we have. We should certainly guard lest in our efforts to make genetic advice too readily available we dilute the quality to the point where we are not achieving the ends we hope to achieve. Man has done fairly well for a good many thousands of years in the absence of genetic counseling, and I'm confident that he probably could forego our pearls of wisdom for another ten or twenty years, until we have the personnel that we need to do an adequate job.

There is a corollary to the problem posed by Dr. Warkany which has nothing to do with geography, and it is this: At a counseling center should we attempt to advise everyone who seeks our counsel? A categorical answer to this is clearly not possible because of the numerous "gray areas" which arise. Let me illustrate one such. Not infrequently, in cases that come to us on our service, we find that the pediatrician, say, if the proband is a child, has decided that the family needs guidance, and that they need the guidance now. Unfortunately, a firm diagnosis on the child has not been reached, but the diagnosis has been narrowed to two or three alternatives. We are strongly encouraged to attempt to give advice to the family. Yet, our advice, obviously, can only be of meaning if we know precisely what the diagnosis is. If one attempts to give advice under these circumstances, he generally tries to advise for all possible contingencies, which then means recognizing, as possible, any one of the diagnoses. The advice then lacks immediacy and is of dubious value to the family. Moreover, the attempt to advise can be very traumatic not only to the genetic counselor but to the family and to the pediatrician, in this instance, as well. While it would seem obvious that one would give no advice in this situation, I know that I have been guilty and I would like to think my colleagues have also been lax in this respect. Perhaps, this is misplaced compassion.

Finally, in summarizing these meanderings, let me emphasize a point that previous speakers have made. Genetic counseling is certainly a very imperfect art even in the hands of the very best of us and is apt to remain so for some time to come. We should be tolerant, therefore, of other genetic counselors who are giving advice in situations which may seem somewhat less than favorable in our eyes.

DR. NEEL: I just want to clarify one point that Dr. Schull made, a point that I'm sure you will encounter if you are engaged in organizing a counseling service.

Our service, as Dr. Schull said, is within the framework of the Out-Patient Clinic of the University Hospital. We occupy space in an out-patient clinic. This is fine. It puts us next to our materials, so to speak. It puts us in a hospital atmosphere, which has many advantages. It also puts us in close proximity to the hospital administrator, and hospital administrators look at space as something which should bring in revenue.

We have worked out a compromise. Everyone who comes to University Hospital pays a registration fee of $5 to $7, in return for which, beyond simple registration, he has a chest film, hemoglobin determination, and serological test for syphilis. Persons registering on our service pay that fee, but they pay no fee for the services rendered by the clinic personnel. If they are referred to neurology or orthopedics, there is, of course, a second fee, the magnitude of which depends on what the service does. So, we have a compromise which satisfies our hospital administrator but certainly does not enrich the Department of Human Genetics.

CHAIRMAN GLASS: Would you like to say something about empiric risk calculations, Dr. Reed?

DR. REED: No. I don't know that I have anything that I would like to say about that, but a setup in which there is an affected parent,

I do have something that has bothered me for a very long time which is concerned with genetic counseling. When the day comes when we have information about the heterozygote, how are we going to answer these questions?

In any study in neurological diseases you know that the age of incidence is rather young, so you can expect that unless a person with a dominant gene has an automobile accident, or something like that, he will live to face the risk of 50 per cent that he will develop the disease.

Now, the day will come, I suspect, when the person carrying this gene—and here the people with the disease are heterozygotes, of course, for the homozygote isn't known — the day will come when it will be possible to predict that a certain individual is going to have this disease. We can also predict that three sisters are not going to have the disease, and one of their brothers, maybe, is. The problem of counseling here is: Can you benefit the people who are not going to have the disease by telling them that they are not? The whole sibship, without question, has anxiety about this. They are always perturbed that they may develop the disease. They may not do anything about it. They may have more children because of it—I don't know—but at any rate it is a problem, because how are you going to tell the three individuals that are not going to get the disease and refuse to say anything to the one that is going to get it? Obviously, if you refuse to tell him anything and you tell his sister something, he would conclude that he is going to get the disease.

I have been exploring this for a long time with our Department of Psychiatry, and I have realized that this is a couch problem — to see what they say, how they would go about this —and suppose we have a technique for distinguishing the heterozygote right now, and we are ready to tell the individuals "Yes, you have the gene. You will get the disease unless you drop dead tomorrow."

What kind of counseling can you give them? Unfortunately, the Department of Psychiatry has not been helpful on this. "We don't have any idea so far," they say, and I realize there is a great deal which must be done in psychiatry to be ready to meet problems of this sort, which will be, really, the $64 questions because there are plenty of families which have this sort of and there is a sibship or young people who are thinking about getting married.

The actualities of what they do are not always the same as what they propose, naturally, and in a family that we had some discussion with, one of the girls said she thought that if she had this gene she would certainly become a nun. Well, six months later she was married. She didn't become a nun, and she has had a couple of children.

In other words, she didn't know whether she was a carrier of the gene or not, but, on the other hand, she didn't consider the situation serious enough to become a nun, which she might have done if she had been certain that she had the gene for the disease.

Anyway, it's certainly a problem for psychiatry, and I suspect it will have to be faced up to before long.

CHAIRMAN GLASS: Dr. Kallmann, do you want to comment on that?

DR. KALLMANN: I don't want to comment on the activities or attitudes of the Department of Psychiatry at the University of Minnesota, but I would like to make a few general statements.

I think we should distinguish between plans for a genetic information center and those for a genetic counseling center. If someone from Arizona writes and wants to find out what is known about the genetic aspects of Tay-Sachs disease or some other disease, and if the given information is supplied by letter, I haven't done any counseling. I have provided information.

My concept of genetic counseling refers to requests for guidance in the presence of familial disease, and this kind of activity should, in my opinion, not be handled in an impersonal way. We have to know the people and their personalities and their family situations before we give counsel.

Nor do I think that genetic counseling is always a one-shot proposition. It may not be possible to give all the required guidance in one session. We have had no difficulty in getting people back after six months or a year. Sometimes we make regular appointments with them and have had little trouble in obtaining

the cooperation of the given families for this purpose.

There's only one other point I want to make. Medical genetics, to me is as important a specialty as radiology or psychoanalysis or any other professional service. It requires a highly specialized kind of knowledge and experience. I don't think that the majority of general practitioners can be expected to have the degree of specialized training which is necessary for counseling purposes. What they should know is where they can get competent advice as to the genetic aspects of a family's problem. Therefore, I question the advisability of leaving the bulk of genetic counseling to the family physician, unless he had some special training.

I think that there should be departments of medical genetics, preferably in every state or in several areas of a large state. Of course, the public, the public health agencies, other medical specialists, and the general practitioners in the state should know where they can obtain specialized advice in relation to genetic problems that are encountered in families under their care.

Often I offer advice as to inheritance problems in the frame of our departmental activities; I do not render it as a practicing psychiatrist. Although I have a couch in my office, it is not being used for counseling procedures, I give this kind of advice as a geneticist who also happens to be a qualified psychiatrist.

DR. MADGE MACKLIN: This morning there was discussion about traits which might have been induced by some environmental factor, and hence not genetically determined. As Dr. Falls has pointed out, some of these so-called environmental traits may arise only in those individuals whose genetic background permits of their appearance. Hence such traits might easily be repeated in the family, although outwardly conditioned by extraneous factors.

I want to speak for a moment about traits which may be conditioned wholly by environmental factors, but for which the specific environment producing them has not been identified. We are unable to point to any extraneous factor which might be responsible for the trait, but we are equally unable to state that this is genetically determined, so we assume that an environmental factor must be at fault. Under such circumstances the onus of proof should rest just as heavily upon the person postulating extraneous factors as upon the person assuming a genetic basis. Since we are unable to identify the specific environment that was responsible for the defect, we cannot warn the parents against encountering the same environment during the next pregnancy. They unwittingly ran into it the first time; they are equally liable to run into it again. Hence, even environmentally induced traits may be repeated in subsequent children, and we should be wary of assuring them that the defect cannot happen again.

How should we advise parents who come with a child suffering from a condition which might be either environmental or genetic or both in origin? Here I want heartily to endorse what Dr. Falls has said. He has a very sane approach. We must take into consideration not only the trait but the parents and family of the child with the trait, their financial, intellectual, emotional and health status. What I would give as advice to emotionally stable, financially secure and intelligent parents of a child with a defect lethal shortly after birth would be very different from what I would give to parents of a similar child whose intelligence was low, who were unable to finance further unrewarding pregnancies, and whose emotional balance could not stand the strain of another defective child.

Even with an excellent family set-up, the advice will differ according to the trait. If the trait is lethal at birth or shortly after, the only ones to suffer are the parents, and they may be advised to continue until they have a normal child. If the trait is one which allows the child to live, a burden to himself as well as others, the parents should have these facts presented.

One more thing I should like to say. Dr. Kallmann has said that the fear of cancer is just as dangerous as cancer itself. I would like to ask him what are the mortality statistics on the number of people who have died of fear of cancer. I already have the mortality statistics for persons in the United States who have died of cancer.

DR. KALLMANN: I don't think one has to be a psychiatrist in order to know that fears may

cause a lot of misery, to the extent of crippling people and turning them into invalids. I did not say that the fear of cancer kills anybody. What I did say was that fear of cancer may be as bad as having cancer. So, I don't think I have to supply any statistics on the mortality of the fear of cancer.

MR. OSBORN: I'd like to supplement briefly what Dr. Falls said.

We are operating today in a society which is not eugenically oriented, and we are operating in a field in which the scientific pace is not sufficient. Even if everybody in every heredity center took the position that they were going to insist on the patient's following the advice which they thought most eugenic, the actual effect would be very, very small, of course—almost so small as to be of no importance whatever.

I have no doubt that the orientation of the public over time will be changed, just as it has been changed in regard to inoculation against contagious diseases. I have no doubt that the scientific base will be strengthened.

I think those who are interested in eugenics would be wise to be patient until both those things has come to pass. Otherwise, we would again do as eugenics did 30 or 40 years ago, espouse things which were not justified, and would turn public opinion back against eugenics.

Since the President of the Eugenics Society, Dr. Harry L. Shapiro, had to leave, may I express our deep appreciation and enthusiasm for the interest and size of the audience, and for those who took part in the discussion. I think it's extraordinary that with the very numerous papers, which met a very crowded schedule, everybody kept exactly within his time limit. This augurs well for the intelligence of the counseling, and it's certainly a very fine thing.

CHAIRMAN GLASS: I'm sure we could continue for some time. I have several questions myself about why my experience of getting such hosts of questions about the dangers of radiation isn't reflected by the other members of the panel; and, again, whether there is any difference between the legal and the personal responsibilities involved when you get asked about the hazards of radiation by mail and when you get requests for counseling in regard to some possibly genetically caused disease.

However, I see we are just not going to have time for an extended discussion. So, regretfully, I think we'll have to call our discussion to a close and thank the members of the panel and the discussants for their part in it.

LETTERS

To The Editor:

I should like to take this opportunity to thank the American Eugenics Society for the opportunity of attending the Heredity Counseling Symposium in New York City on November 1st. I found the presentations and discussions highly informative and stimulating. There was, however, a question running persistently through the day's discussions, which I felt was only partly asked and, therefore, only partly answered.

The question I would have liked to hear clearly stated, and perhaps hotly debated, is this: What constitutes *success* in genetic counseling?

Now it will be clear to those who heard the discussion on this occasion that much that was said at the symposium helps us to find a satisfactory answer to this question. On the other hand, I know of no way to bring this question into sharper focus than to ask a second question: What *need* is met by genetic counseling? And for me the answer to the first question is to be found in the answer to the second.

Clients seek genetic counseling for a variety of reasons: sometimes for moral support or emotional support, sometimes for information, sometimes for real advice as to how to regulate their lives from a genetic standpoint. I am completely satisfied that the need of the patient for support and for guidance is best met when the issues at stake are most fully understood from a genetic standpoint, and I agree wholeheartedly with Dr. Falls who pointed out that our understanding must include a full realization and sharing of what we do *not* know as well as what is available to us as factual knowledge in the area of human genetics. On the other hand, I feel that it is of the utmost importance that we distinguish clearly between *genetic science* and *genetic counseling*. In my opinion the calculation of empiric risk figures, gene frequencies, and the like, belongs to genetic science rather than to genetic counseling, though they form an essential part of the factual background against which genetic counseling takes place.

I would like particularly to suggest that empiric risk figures are of limited use to genetic counseling and that the success of genetic counseling is scarcely to be realized in the tailoring of reproductive activity to such figures. At every level of genetic risk, I am sure, there are both decisions for and decisions against participation in genetic gambles which are valid and proper expressions of the lives of persons involved.

There is a further sense, I think, in which we may see the limitations of empiric risk figures, and that is to point out that in reality they have little to do with the evolution of any given clinical problem. The risk figure for any clinical problem might be said to be 50 per cent inasmuch as it will either resolve itself satisfactorily or badly. Regardless of how unlikely the second eventuality may be from a purely statistical standpoint, it remains a real potentiality and will be the result of a losing gamble. I think it fair to point out to clients that if they cannot under any circumstances afford to lose, even to a very long shot, they should not be in the game. On the other hand, as Dr. Falls suggested, sometimes, where risks are relatively high, mature people with the resources which permit them to cope with losses will regard the acceptance of these risks as the most constructive use they can make of their lives. Failure to accept a small risk can oftentimes be regarded as equally constructive. Dr. Kallmann said all this much better than I can in pointing out the necessity for knowing the background of potential difficulty not just with respect to the genetic trait but most especially with respect to the structure of the family that carries it. Only with this kind of understanding can the genetic counselor guide his clients to the choices which are *right* for *them*.

I would welcome discussion or debate on any of the points I have raised in this letter.

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